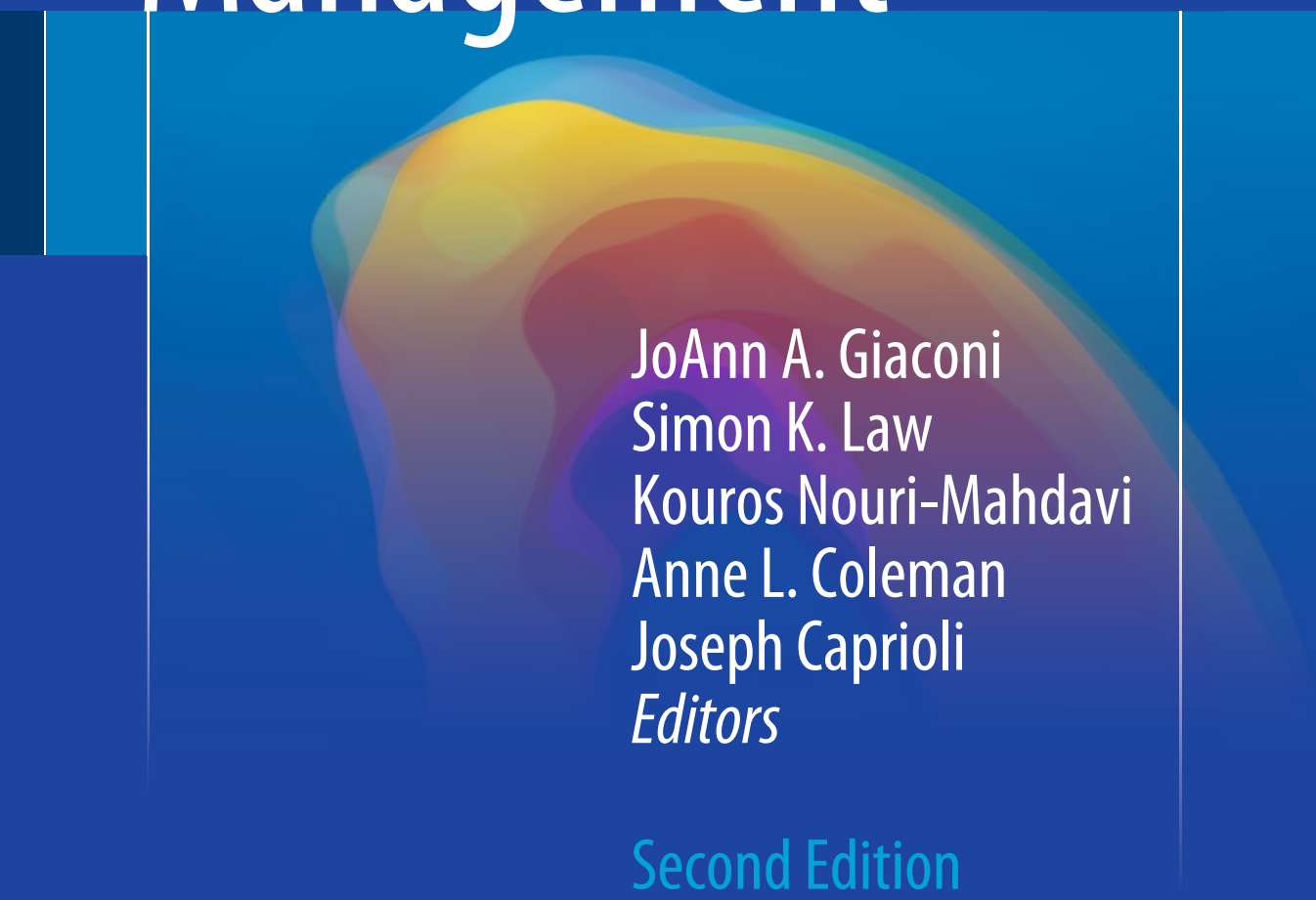
Pearls of Glaucoma Management



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Editors

Second Edition

Springer

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Foreword

If you have ever uttered the commonly expressed lament, "Glaucoma is so confusing!" then this text is for you. You will no longer be bewildered.

Why practitioners may be confused about how to be of help to patients with glaucoma—in its many incarnations and reincarnations—is easily understood. The issue seems to be overwhelming when one considers that the already massive population of those with glaucoma is increasing rapidly as the world's population increases and ages.

During the past 50 years the fundamental definition of glaucoma has changed almost 180°, and the indications for treatment have become more variable and controversial, some advising early therapy and others strongly cautioning against such an approach: Various diagnostic tests have come and gone and are interpreted in such different ways that there seems to be no consensus; surgical techniques come in and out of fashion in perplexing ways. There seems to be a constantly shifting, sandy foundation on which are built unsteady schools of ever-varying advice. Why practitioners, patients, and the public are often bewildered is understandable.

The current text was designed to be relevant, scientific, and practical. The editors have accomplished their objective well. The authors chosen to share their wisdom are expert practitioners who recognize the dangers of basing treatment on theory. They, the leaders in their fields, create an understanding of glaucoma and conditions related to glaucoma that is sound, scientific, and effective. The editors clearly instructed their contributors to avoid speculation, to be practical, and to insist on evidence, not opinion (and where good evidence was lacking, to indicate such a lack). The result is a cohesive picture that should be of immense help to all those trying to make sense of what to many seems to be confusing.

It is perhaps not surprising that this text accomplishes its objective so admirably. The senior editor is a vastly experienced physician, equally at home in the clinic, the operating room, the classroom, and in a basic research laboratory. The contributing authors come from many different institutions and cultures; some are younger and others older. The current text, however, does not present information that must be sifted by a discerning reader in order to come up with appropriate advice. Rather, the authors simplify, clarify, organize, and explain practically and scientifically. Those wanting to know how to approach patients with glaucoma or those many, many patients in whom it is not clear whether glaucoma is present or not will find this a treasure trove of sound science blended with critical experience.

The need for this intellectually vigorous, practical approach to caring for patients with conditions related to intraocular pressure and optic nerve disease is great. There is probably truth in the belief that all persons will eventually develop glaucoma if they live long enough. As the world population ages and increases, as resources become ever more precious, and as cost considerations become more confining, there is increasing urgency for guidelines that concentrate on the essentials and that will help achieve the goal of caring for the sick and for the well, specifically, the greatest good for the greatest number, while still addressing the needs and wants of each individual person.

Currently there is much interest in "translational research." This book is highly successful in translating vast amounts of disparate, sometimes disconcerting information into understandable sentences, paragraphs, and illustrations that will result in more effective and more relevant care.

Philadelphia, PA, USA George Spaeth

Preface

This book was developed based on the questions that clinicians, fellows, and residents taking care of glaucoma patients have asked us as consultants. Most textbooks on glaucoma provide a broad overview of the clinical and basic science literature, which is very useful to students learning about glaucoma. However, these textbooks may leave many questions unanswered for the clinician searching for advice on how to manage a specific problem. This book asks and answers those questions. Additionally, it covers topics that are not always included in traditional textbooks but that are being discussed at national and international meetings.

In addition to asking the questions that frequently arise in managing patients with glaucoma, a goal of this textbook was to have the authors who are familiar with the world literature digest that information in the context of their own clinical experience. We asked authors to answer questions the way they might answer a physician's questions over the phone. We asked them to state their opinions on how they like to manage clinical situations, where appropriate, and to also point out that their preferred management is not the only way to manage the problem if other acceptable means are available. The questions are organized by topic and cover diagnostic testing and interpretation, risk factors, medical treatment, procedural treatments, various glaucoma subtypes, and complications.

We must thank all the consulting physicians, students, residents, and fellows who we have encountered and who inspired this textbook. As well, we thank Ms. Minn Oh for administrative help with the second edition of this book.

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Optic Nerve: The Glaucomatous Optic Nerve

1

Claude F. Burgoyne

Core Messages

- The principle insult in glaucoma occurs within the neural, cellular, and connective tissues of the optic nerve head (ONH).
- Intraocular pressure at all levels has biomechanical effects on the optic nerve tissues.
- Clinical cupping is one manifestation of the pathophysiology of glaucomatous damage, but is not the pathophysiology itself.
- The variable appearance of the ONH in all optic neuropathies is the predictable result of ONH tissue biomechanics.
- As our clinical tools for characterizing ONH biomechanics improve, so too will our ability to understand normal ONH aging and its contributions to the clinical behavior and susceptibility of the ONH.

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1.1 Why Is the Optic Nerve Important in the Diagnosis and Management of Glaucoma?

Glaucoma is an optic neuropathy. Although there are several pathophysiologies that must be managed in the clinical care of the glaucoma patient, what defines all forms of glaucoma is an optic neuropathy that demonstrates classic and recognizably variable [1–6] structural and functional behaviors.

1.1.1 The Optic Nerve Head Is the Principal Site of Glaucomatous Damage to the Visual System

Although glaucomatous damage likely encompasses important pathophysiology within the retinal ganglion cell (RGC) stroma [7–12], photoreceptors [13–17], lateral geniculate body [18–20], and visual cortex [20], strong evidence suggests that damage to the RGC axons within the lamina cribrosa of the optic nerve head (ONH) [21–26] is the central pathophysiology underlying glaucomatous vision loss. Recent studies in monkeys [25–30], rats [31–33], and mice [34] support the importance of the ONH in glaucoma by describing profound alterations at

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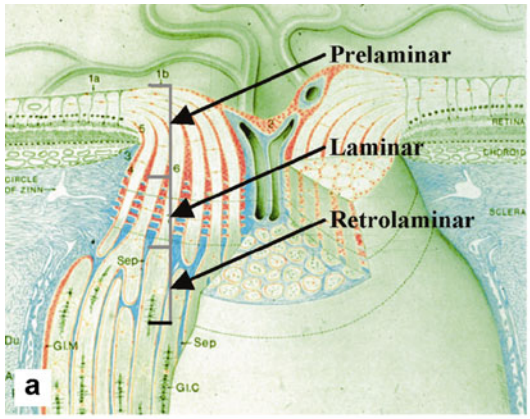
the earliest detectable stage of the disease within the prelaminar, laminar, and peripapillary scleral tissues of the ONH.

The ONH tissues make up a dynamic environment wherein 1.2–2.0 million RGC axons converge, turn, and exit the eye through the inner (Bruch's membrane opening) and outer (scleral) portions of the neural canal (Fig. 1.1). Within the scleral portion of the canal, the bundled axons pass through a three-dimensional meshwork of astrocyte-covered, capillary-containing connective tissue beams known as the lamina cribrosa (Fig. 1.1). Within the lamina, axonal nutrition is dependant upon the movement of oxygen and nutrients from the laminar capillaries, through the laminar beam extracellular matrix (ECM), into the laminar astrocyte processes within the beam, finally reaching the peripheral and central axons of each bundle, via cell processes [35].

The connective tissue beams of the lamina cribrosa are anchored via the neural canal wall to a circumferential ring of collagen and elastin fibers within the peripapillary sclera [36–38] and are presumed to bear the forces generated by intraocular pressure (IOP) (Fig. 1.1). IOP-related stress (force/cross-sectional area of the tissue experiencing that force) and strain (a measure of local deformation of a tissue induced by applied stress) within the load-bearing tissues of the ONH influence the physiology and pathophysiology of all three ONH tissue types (Table 1.1): (1) the connective tissues, (2) the neural tissues, and (3) the cells that exist alone or in contact with both (1) and (2) [39–41].

While the pathophysiology of glaucomatous damage to the ONH tissues remains controversial, we have proposed that it is multifactorial and is influenced by at least three etiologies (Table 1.2)—IOP-related connective tissue stress and strain [21–24], blood flow/nutrient diffusion/ischemia within the laminar and prelaminar tissues [42–45], and the autoimmune and/or inflammatory state of the tissues [46–51] (Fig. 1.2, top). The interplay between the pathophysiology of ONH neural and connective tissue damage and the clinical appearance and behavior of the neuropathy are discussed in Figs. 1.2 and 1.3 and the sections that follow.

Fig. 1.1 The optic nerve head (ONH) is centrally influenced by IOP-related stress and strain. The ONH is made up of prelaminar, laminar, and retrolaminar regions (**a**). Within the clinically visible surface of the normal ONH (referred to as the optic disc) (**b**), central retinal vessels enter the eye and retinal ganglion cell (RGC) axons appear *pink* because of their capillaries (which are principally supplied by branches from the posterior ciliary arteries (PCA) in (**c**). The primary site of RGC axon insult in Glaucoma is within the lamina cribrosa (schematically depicted with axon bundles) in (**d**), isolated by trypsin digest in a scanning electron micrograph in (**e**) and drawn with stippled extracellular matrix (ECM), central capillary (*red*), and surrounding astrocytes (*yellow* with basement membranes in *black*) (**f**). Blood flow within the ONH, while controlled by autoregulation, can be affected by non-IOP-related effects such as systemic blood pressure fluctuation and vasospasm within the retrobulbar portion of the PCAs. Additional IOP-induced effects may include compression of PCA branches within the peripapillary sclera (due to scleral stress and strain) and compression of laminar beam capillaries reducing laminar capillary volume flow (**c**, **f**) [43]. There is no direct blood supply to the axons within the laminar region. Axonal nutrition within the lamina (**f**) requires diffusion of nutrients from the laminar capillaries, across the endothelial and pericyte basement membranes, through the ECM of the laminar beam, into astrocyte processes within the beam, through the astrocyte processes into the adjacent axons (*vertical lines*). Chronic age-related changes in the endothelial cell and astrocyte basement membranes, as well as IOP-induced changes in the laminar ECM and astrocyte basement membranes may diminish nutrient diffusion to the axons in the presence of a stable level of laminar capillary volume flow. The clinical manifestation of IOP-induced damage to the ONH is most commonly "deep cupping" (**g**), but in some eyes cupping can be shallower accompanied by pallor (**h**). *Z-H* circle of Zinn-Haller; *PCA* posterior ciliary arteries; *NFL* nerve fiber layer; *PLC* prelaminar region; *LC* lamina cribrosa; *RLC* retrolaminar region; *ON* optic nerve; *CRA* central retinal artery. (**a**) Reproduced with permission of Arch Ophthalmol. Copyright 1969 American Medical Association. All Rights reserved [35]. (**b**, **g**, **h**) Reprinted with permission from J Glaucoma. Copyright 2008 [83]. (**c**) Reprinted with permission from Elsevier. Copyright 1996. This article was published in The Glaucomas. Edited by Ritch R, Shields MB, Krupin T. Mosby, St. Louis; Cioffi GA, Van Buskirk EM: Vasculature of the anterior optic nerve and peripapillary choroid. Pg 177–197 [140]. (**d**) Courtesy of Harry A. Quigley and reprinted with permission from Kugler Publications, Amsterdam [141]. (**e**) Reproduced with permission of Arch Ophthalmol. Copyright 1990 American Medical Association. All Rights reserved. (**f**) Reproduced with permission of Arch Ophthalmol. Copyright 1989 American Medical Association. All Rights reserved [142]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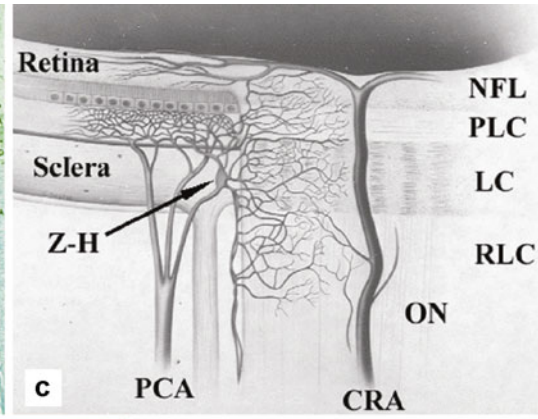
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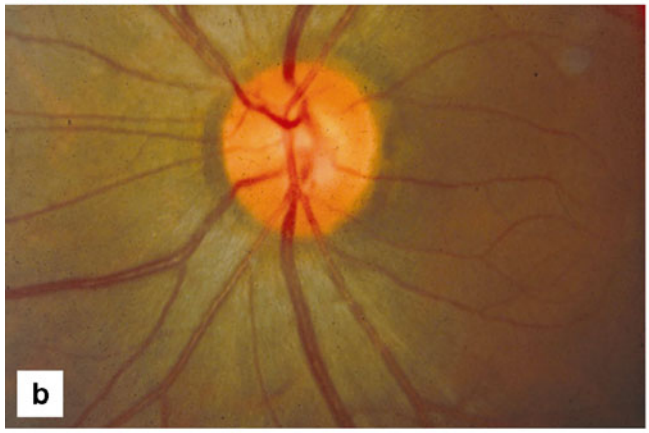
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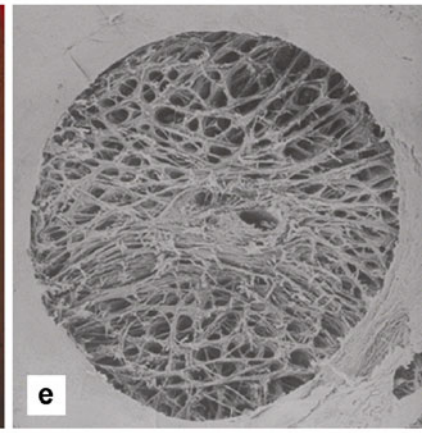
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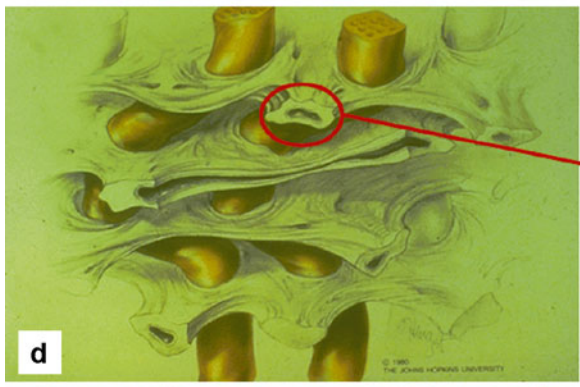
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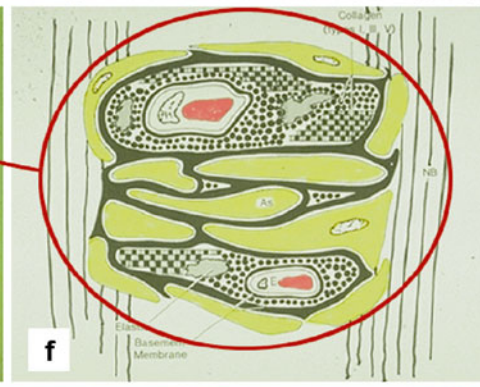
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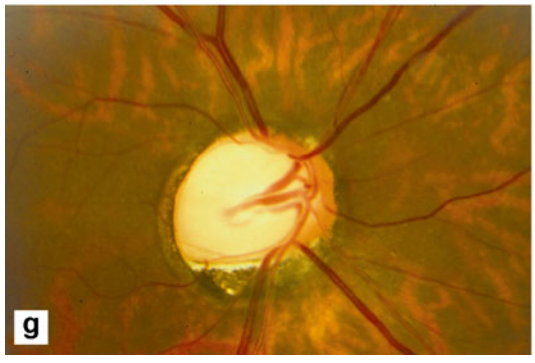
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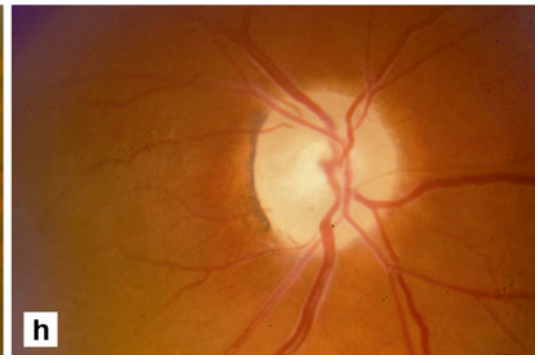
h

Table 1.1 Optic nerve head tissue types

1.	Connective tissues
	Load-bearing connective tissues of the peripapillary sclera, scleral canal wall, and lamina cribrosa
2.	Neural tissues
	Retinal ganglion cell (RGC) axons
3.	Cells that exist alone or in contact with 1 and 2 above
	Astrocytes
	Glial cells
	Endothelial cells
	Pericytes
	Basement membranes (BM)

Table 1.2 Primary proposed etiologies glaucomatous damage to the ONH

IOP-related connective tissue stress and strain
Blood flow/nutrient diffusion and/or ischemia within the laminar and prelaminar tissues
Autoimmune and/or inflammatory mechanisms within the tissue

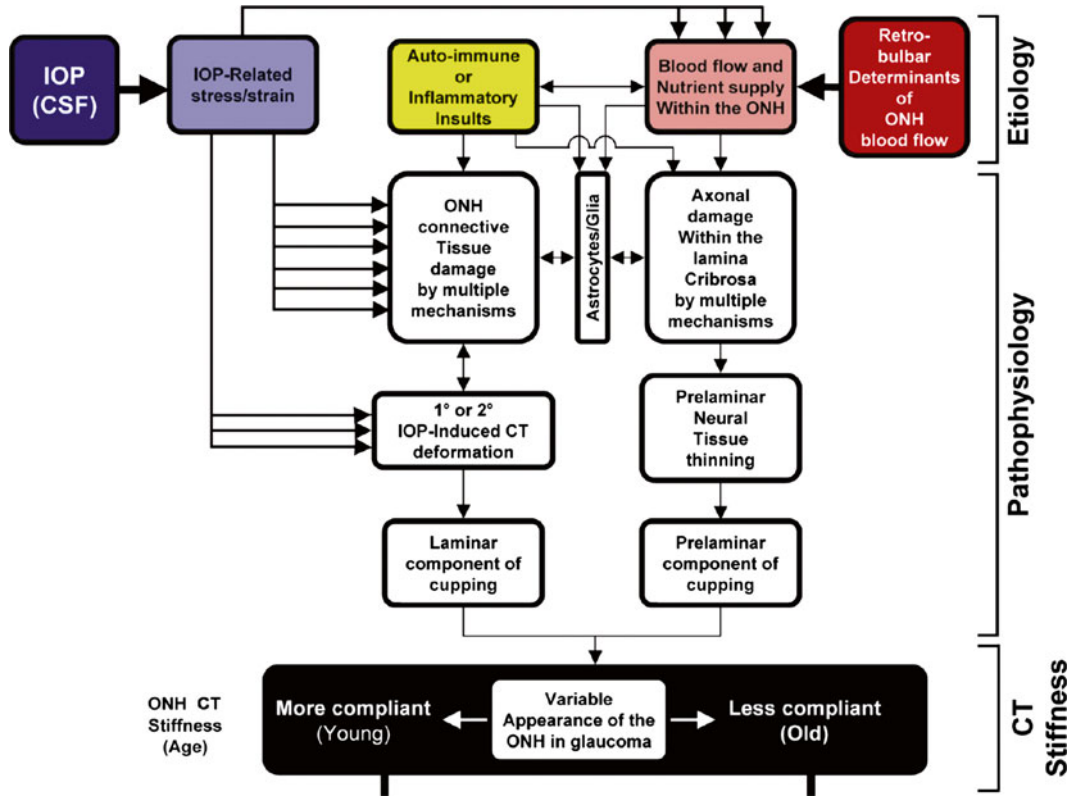

Fig. 1.2 While damage to the neural and connective tissues of the ONH is multifactorial, ONH appearance in the neuropathy is importantly influenced by connective tissue stiffness. In our biomechanical paradigm, IOP-related strain influences the ONH connective tissues and the volume flow of blood (primarily) and the delivery of nutrients (secondarily), through chronic alterations in connective tissue stiffness and diffusion properties (explained in Fig. 1.1). Non-IOP-related effects such as autoimmune or inflammatory insults (*yellow*) and retrobulbar determinants of ocular blood flow (*red*) can primarily damage the ONH connective tissues and/or axons, leaving them vulnerable to secondary damage by IOP-related mechanisms at normal or elevated levels of IOP. Once damaged, the ONH connective tissues can become more or less rigid depending upon lamina cribrosa astrocyte and glial response. If weakened, ONH connective tissues deform in a predictable manner, which underlies a laminar component of clinical cupping (Figs. 1.3 and 1.4). Reprinted with permission from J Glaucoma, copyright 2008 [83]

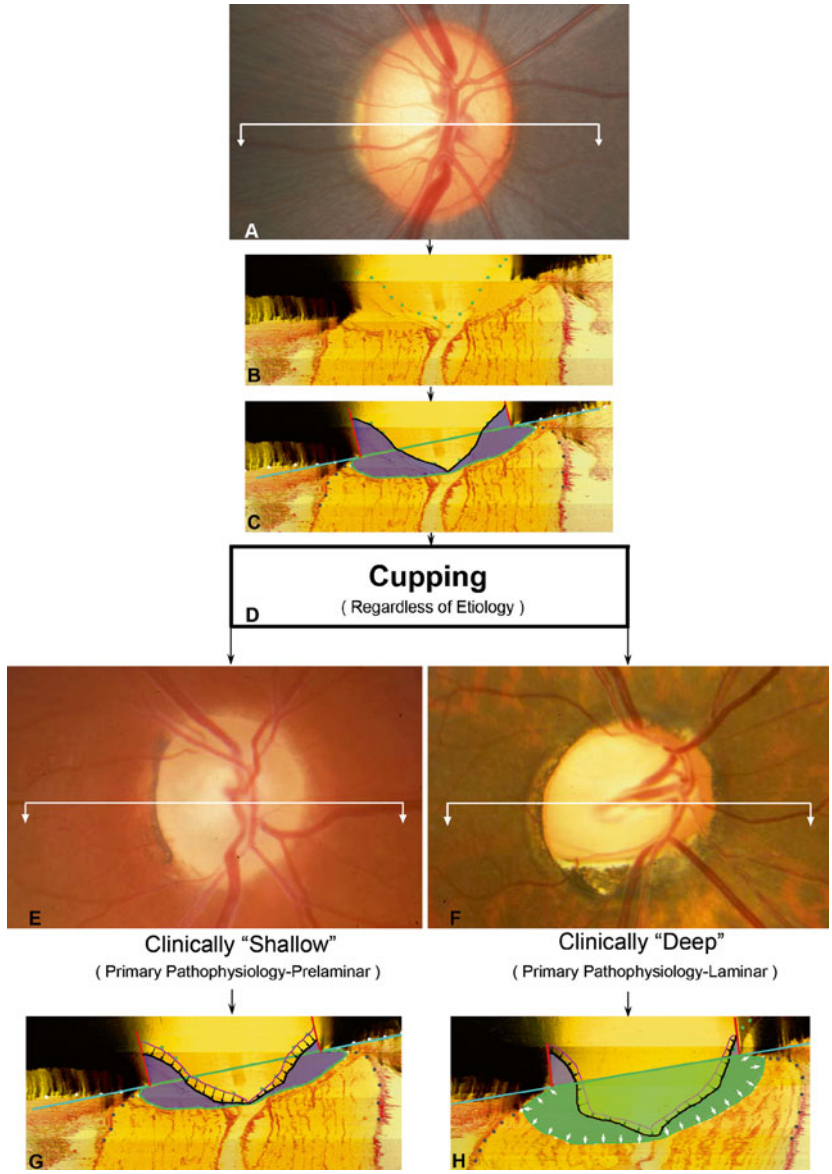

Fig. 1.3 All clinical cupping, regardless of etiology, is a manifestation of underlying "prelaminar" and "laminar" pathophysiologic components. (**a**) Normal ONH. To understand the two pathophysiologic components of clinical cupping, start with (**b**) a representative digital central horizontal section image from a postmortem 3D reconstruction of this same eye (*white section line* in (**a**))—vitreous top, orbital optic nerve bottom, lamina cribrosa between the sclera and internal limiting membrane (ILM) delineated with *green dots*. (**c**) The same section is delineated into principle surfaces and volumes (*black*—ILM; *purple*—prelaminar neural and vascular tissue; *cyan blue line*—bruchs membrane opening (BMO)-zero reference plane cut in section; *green outline*—post-BMO total prelaminar area or a measure of the space below BMO and the anterior laminar surface). (**d**) Regardless of the etiology, clinical cupping can be "shallow" (**e**) or "deep" (**f**) (these clinical photos are representative and are not of the eye in (**a**)). A prelaminar or "shallow" form of cupping (**g**, *black arrows*) is primarily due to loss (thinning) of prelaminar neural tissues without important laminar or ONH connective tissue involvement. Laminar or "deep" cupping (**h**, *small white arrows* depict expansion of the *green shaded space*) follows ONH connective tissue damage and deformation that manifests as expansion of the total area beneath BMO, but above the lamina. Notice in (**h**) that while a laminar component of cupping predominates (*white arrows*) there is a prelaminar component as well (*black arrows*). While prelaminar thinning is a manifestation of neural tissue damage alone, we propose that laminar deformation can only occur in the setting of ONH connective tissue damage followed by permanent (fixed) IOP-induced deformation (Reprinted with permission from [30]). Investigative Ophthalmology & Visual Science by Hongli Yang. Copyright 2007 by Investigative Ophthalmology & Visual Science. Reproduced with permission of Investigative Ophthalmology & Visual Science in the format Textbook via Copyright Clearance Center [30]

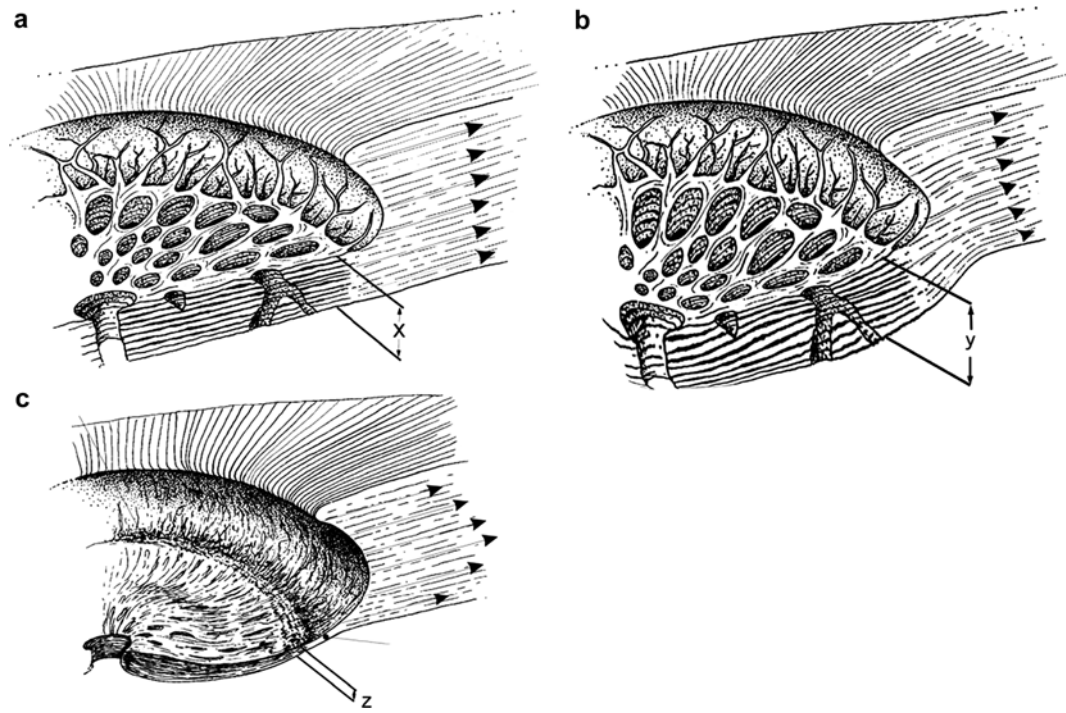

Fig. 1.4 Our central hypothesis regarding ONH connective tissue damage in "laminar" cupping. "Deep," "laminar," or "glaucomatous" cupping is a manifestation of ONH connective tissue damage, which can be caused by either IOP-related or non-IOP-related insults (see Fig. 1.5). However, regardless of the primary insult to the ONH connective tissues, their deformation (if present) is driven by IOP-related connective tissue stress and strain. Thus, the presence of ONH connective tissue deformation in any optic neuropathy is evidence that the level of IOP at which it occurred (whether normal or elevated) is too high for the connective tissues in their present condition. (**a**) Schematic of normal laminar thickness (*x*) within the scleral canal with scleral tensile forces acting on the scleral canal wall. (**b**) Early IOP-related damage in the monkey eye [25–30] includes posterior bowing of the lamina and peripapillary sclera accompanied by neural canal expansion (mostly within the posterior (outer) scleral portion) and thickening (not thinning) of the lamina (*y*). In our studies to date, this appears to represent mechanical yield (permanent stretching) rather than mechanical failure (physical disruption) of the laminar beams (**c**). Progression to end-stage damage includes profound scleral canal wall expansion (clinical excavation) and posterior deformation and thinning of the lamina (*z*) by mechanisms that are as yet uncharacterized [143, 144]. If all other aspects of the neuropathy are identical, the stiffer the lamina, the more resistant it will be to deformation. Whether this is better or worse for the adjacent axons is a separate question that remains to be determined. Reprinted from Prog Retin Eye Res:24. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT: The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage; pp. 39–73. Copyright (2005) with permission from Elsevier [41]

1.1.2 The Pathophysiology of Glaucomatous Damage Is Separate from the Clinical Phenomenon of "Cupping"

Cupping is a clinical term used to describe enlargement of the ONH cup in all forms of optic neuropathy [52–59]. However, *cupping* is also used as a synonym for the pathophysiology of glaucomatous damage to the ONH [24, 60–62]. Because the clinical and pathophysiologic contexts for *cupping* are seldom clarified, there is a confusing literature regarding the presence, importance, and meaning of *cupping* in a variety of optic neuropathies [2, 63–76].

We have previously proposed [30] that all optic neuropathies can demonstrate clinical cupping and that all forms of *clinical* cupping have two principal *pathophysiologic* components—prelaminar thinning and laminar deformation (Fig. 1.3). Prelaminar thinning results from net thinning of the prelaminar tissues due to physical compression and/or loss of RGC axons even in the presence of gliosis [77–80]. In this paradigm, prelaminar thinning results in a clinically shallow form of cupping [81, 82] (being limited to the prelaminar tissues) that occurs in all forms of RGC axon loss (including aging) and is therefore nonspecific. Laminar deformation results in a clinically deeper form of cupping that occurs only in those optic neuropathies in which damaged ONH connective tissues (lamina cribrosa and peripapillary scleral connective tissue) have become susceptible to permanent, IOP-induced deformation [25, 26, 28, 29, 41]. Whether the ONH connective tissues are primarily damaged by IOP or some other insult (ischemic, autoimmune, inflammatory, secondary astrocyte activation, or genetic predisposition [41]) (Fig. 1.4), if they deform they do so under the effects of IOP (normal or elevated) in a predictable way, and this deformation underlies laminar or deep or glaucomatous cupping (Figs. 1.3 and 1.4).

The previous paragraph contains two important ideas. First, it is possible for non-IOP-related processes to damage the ONH primarily and still end up with a nerve that looks and behaves in a manner we call *glaucomatous*. Second, IOP-related connective tissue stress and strain still drive the processes that cause the damaged tissues to deform, even if IOP is not the primary insult in the process and regardless of whether IOP is high or low.

1.1.3 The Clinical Appearance and Behavior of the ONH Holds Clues as to the Etiology of a Given Optic Neuropathy

When IOP is not elevated, and sometimes even when it is, the clinical challenge in the examination of the optic disc is not to recognize glaucoma, but rather to recognize the presence of an optic neuropathy and then separately determine the likelihood that IOP is playing a contributing role. The notions of laminar and prelaminar cupping suggest two important concepts to consider in the clinical assessment of an optic neuropathy.

First, detection of clinical cupping or its progression suggests the presence of an optic neuropathy, but it does not confirm that IOP is the etiologic agent. Regardless of clinical circumstances, but particularly when IOP is within normal limits, clinical cupping without clinically detectable connective tissue deformation should not be an absolute indication for IOP lowering. We have previously proposed that in patients with robust ONH connective tissues, IOP-related stress and strain can cause a prelaminar form of cupping in which pallor exceeds excavation by causing axonal degeneration without damage to the underlying connective tissues [41, 83]. Having proposed this concept, we now emphasize that without direct evidence of ONH connective tissue damage, the role of IOP in an individual optic neuropathy cannot be certain.

Second, in contrast to surface change detection, clinical detection of ONH connective tissue damage (i.e., a "laminar" contribution to cupping) is direct evidence of IOP involvement in the neuropathy and should become an absolute indication for IOP lowering, regardless of the level of IOP or the etiology of the primary connective tissue insult (ischemia, autoimmune, inflammatory, or IOP-related strain) [41, 83]. Thus, in all eyes, the presence of laminar cupping has diagnostic significance if we can develop the clinical tools to detect it.

1.1.4 The Aged ONH Holds Important Clues About Susceptibility

A variety of data suggest that the ONH becomes more susceptible to progressive glaucomatous damage as it ages, though this concept remains unproven through direct experimentation and it may not hold true for every aged eye. The data to

date can be summarized as follows. First, in most [84–88] but not all [89, 90] population-based studies, IOP does not increase with age, and in some studies where it does increase, the magnitude of increase is not likely to be clinically important. Thus, the fact that the prevalence of glaucoma increases with age [91–93] is likely explained by a greater susceptibility to IOP and other non-IOP-related risk factors, rather than to a higher prevalence of IOP elevation with increasing age. Second, in an extensive review of the literature, low-tension glaucoma is a disease of the elderly [94–99], with only a few reports regarding the onset and progression of normal tension glaucoma in infants, children, and young adults [100]. Third, age is an independent risk factor for both the prevalence [91–93] and progression of the neuropathy at all stages of damage [101–103].

1.1.5 How Age Influences the Susceptibility and Clinical Behavior of the ONH

Over a lifetime, the ONH connective tissues are exposed to substantial levels of IOP-related stress and strain at normal levels of IOP. This stress and strain increases as IOP increases and/or fluctuates (Fig. 1.5) [104–108]. Stresses and strains at a given level of IOP are physiologic or pathophysiologic depending upon the response of the tissues that experience them (Fig. 1.5). In this context, IOP is not so much normal as physiologic or pathophysiologic and what constitutes physiologic and pathophysiologic levels for IOP may change as they are influenced by associated systemic factors and aging.

Physiologic stress and strain induce a broad spectrum of changes in both the connective

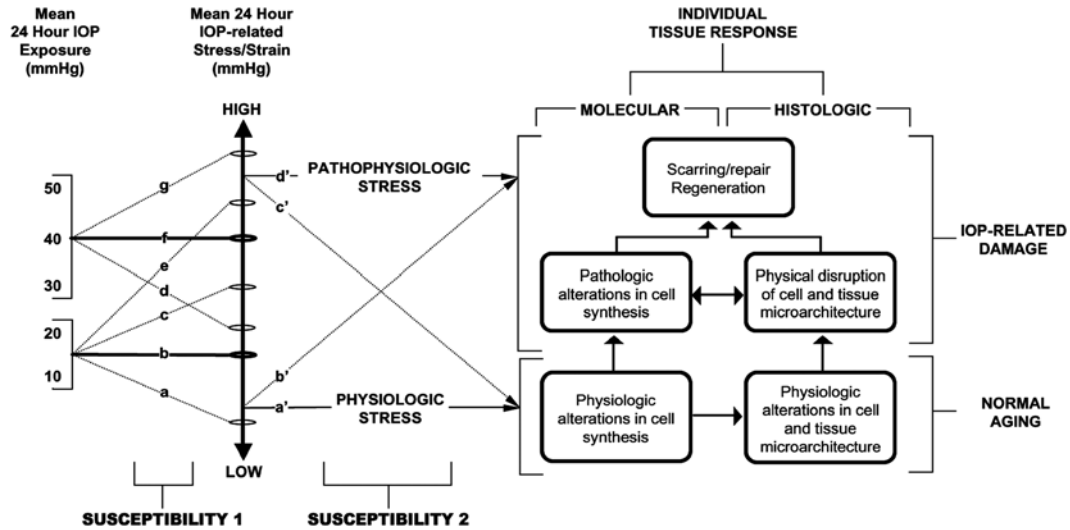

Fig. 1.5 Over the course of a lifetime, whether an eye demonstrates the "neuropathy of aging" or the neuropathy of glaucoma lies in ONH susceptibility. For a given ONH, IOP generates low or high levels of stress depending upon the 3D architecture of the ONH connective tissues (size and shape of the canal, thickness of the lamina and sclera—*susceptibility 1*). Some ONHs will have relatively low stress at high IOP (*d*). Others will have high stress at low IOP (*e*). Whether a given level of IOP-related stress is physiologic or pathophysiologic depends upon the ONH's microenvironment (*susceptibility 2*). Strong connective tissues, a robust blood supply, and stable astrocytes and glia increase the chance of normal ONH aging (*right*, *bottom*). While the existence of a neuropathy of aging is controversial, the difference between "normal" age-related axon loss (if it is shown to exist) and the development of glaucomatous damage is a matter of ONH susceptibility (Reprinted with permission from [41]). Reprinted from Prog Retin Eye Res:24. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT: The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage; pp. 39–73. Copyright (2005) with permission from Elsevier [41]

tissues and vasculature that are central to normal aging. While the concepts of age-related optic nerve axon loss [33, 109–114] and an optic neuropathy of aging [2, 55, 113–115] remain controversial, we believe that the range of physiologic stress and strain experienced within the ONH connective tissues over a lifetime are likely to be of central importance to both concepts.

Pathophysiologic stress and strain induce pathologic changes in cell synthesis and tissue microarchitecture (Fig. 1.5) that exceed the effects of aging. These changes underlie two governing pathophysiologies in glaucoma: (1) mechanical yield and/or failure of the load-bearing ONH connective tissues (Figs. 1.2, 1.3, and 1.4), and (2) progressive damage to the adjacent axons by a variety of mechanisms (Fig. 1.2).

The aged ONH is more likely to have stiff connective tissues [116–128] and a compromised blood supply [129, 130]. However, age-related increases in laminar beam thickness [117, 120, 122, 127, 131], laminar astrocyte basement membrane thickness [120, 131], and laminar ECM hardening [117, 120, 122, 131] should not only increase laminar beam stiffness, but should also diminish nutrient diffusion from the laminar capillaries into adjacent axons (Fig. 1.1). Thus, for a given magnitude of IOP insult, the aged ONH should demonstrate (1) less deformation due to the presence of a stiffer lamina and peripapillary sclera and (2) more pallor for a given amount of deformation because (a) the aged ONH may be more susceptible to axon loss and (b) pallor precedes deformation in the aged eye, while deformation precedes (or supersedes) pallor in the young eye.

Apart from the issue of ONH susceptibility, we predict that if all aspects of insult are equal (alterations in IOP, the volume flow of blood and nutrient transfer from the laminar capillary to the ONH astrocyte are all of the same magnitude, duration, and fluctuation), the aged eye will demonstrate clinical cupping that is on average shallow and pale (at all stages of field loss) compared with the eye of a child or a young adult. This clinical behavior in its most recognizable form is described as *senile sclerotic cupping* [1–6, 132].

We thus propose an overlap between the optic neuropathy of aging and the optic neuropathy of glaucoma in the aged eye and a biomechanical explanation for why the aged eye should demonstrate a shallow form of clinical cupping in which pallor more than deformation predominates.

1.1.6 Apart from the Aged ONH, Are There Some Nerves That Are Mechanically More Sensitive to Damage?

Although IOP [133–136] has been shown to play a causative role in glaucomatous ONH damage at all levels of IOP, many questions remain. There is no agreement on the effects of IOP within the tissues of the ONH; no data exist that would allow one to predict a safe level of IOP for a given ONH; and there are no accepted explanations for the varied clinical manifestations of glaucomatous damage [3], glaucomatous cupping, and glaucomatous visual field loss.

The principal ocular determinants of ONH susceptibility to a given level of IOP are likely to include (1) the IOP level (both the magnitude and variation); (2) the geometry and material properties of the ONH and peripapillary scleral connective tissues; (3) the volume flow and perfusion pressure of blood within the laminar capillaries; (4) nutrient diffusion to the astrocytes for a given level of blood volume and pressure; (5) the molecular response of astrocytes and glia to physical strain within their basement membrane and the presence of physiologic stress within their microenvironment (Fig. 1.2); (6) RGC factors that make its axon more susceptible to damage within the ONH, or its stroma more susceptible to apoptosis in response to axonal distress; (7) the immune environment of the ONH and retina; and (8) the number of remaining viable axons.

At present, we lack the means to directly assess any of the determinants listed above; however, the following features may soon be within the reach of a variety of new imaging strategies and may contribute to clinically derived engineering finite element models of individual

ONHs that we hope will one day underlie target pressure assignment: (1) the three-dimensional geometry and material properties of the lamina cribrosa, scleral flange, and peripapillary sclera [104–108]; (2) the difference in material properties between the peripapillary sclera and the lamina cribrosa [137, 138]; (3) the flow of blood and transport of nutrients across the basement membranes and ECM of the laminar beams; (4) the volume flow of blood through the intrascleral branches of the posterior ciliary arteries; and (5) the presence of peripapillary scleral posterior bowing and the distance between the anterior-most point of the subarachnoid space and the vitreous cavity [139].

Summary for the Clinician

- Glaucoma is an optic neuropathy in which the principal insult to the visual system is multifactorial and occurs within the neural, cellular, and connective tissues of the optic nerve head (ONH).
- IOP is a contributing risk factor to this pathophysiology at low, normal, and elevated levels because of its primary and secondary biomechanical effects on these tissues.
- Clinical cupping is one manifestation of the pathophysiology of glaucomatous damage, but is not the pathophysiology itself.
- A shallow form of cupping is nonspecific and can be expected to occur in all forms of optic neuropathy. Although the clinical appearance and behavior of the neuropathy of glaucoma can vary and include shallow forms of cupping, the pathophysiology of glaucomatous damage classically involves a deep form of cupping, which is a manifestation of ONH connective tissue damage and deformation. The variable appearance of the ONH in all optic neuropathies is the predictable result of ONH tissue biomechanics.
- As our clinical tools for characterizing ONH biomechanics improve, so too will our ability to understand normal ONH aging and its contributions to the clinical behavior and susceptibility of the ONH.

Acknowledgements Portions of this chapter and its figures appeared in the following article and are used with the permission of the *Journal of Glaucoma*:

Burgoyne CF, Downs JC. Premise and Prediction—How Optic Nerve Head Biomechanics Underlies the Susceptibility and Clinical Behavior of the Aged Optic Nerve Head. Invited original article. J Glaucoma 2008;17:318–328.

References

1. Broadway DC, Nicolela MT, Drance SM. Optic disk appearances in primary open-angle glaucoma. Surv Ophthalmol. 1999;43 Suppl 1:S223–43.
2. Jonas JB, Grundler A. Optic disc morphology in "age-related atrophic glaucoma". Graefes Arch Clin Exp Ophthalmol. 1996;234:744–9.
3. Nicolela MT, Drance SM. Various glaucomatous optic nerve appearances: clinical correlations. Ophthalmology. 1996;103:640–9.
4. Nicolela MT, Drance SM, Broadway DC, et al. Agreement among clinicians in the recognition of patterns of optic disk damage in glaucoma. Am J Ophthalmol. 2001;132:836–44.
5. Nicolela MT, McCormick TA, Drance SM, et al. Visual field and optic disc progression in patients with different types of optic disc damage: a longitudinal prospective study. Ophthalmology. 2003;110:2178–84.
6. Nicolela MT, Walman BE, Buckley AR, Drance SM. Various glaucomatous optic nerve appearances. A color Doppler imaging study of retrobulbar circulation. Ophthalmology. 1996;103:1670–9.
7. Asai T, Katsumori N, Mizokami K. Retinal ganglion cell damage in human glaucoma. 2. Studies on damage pattern. Nippon Ganka Gakkai Zasshi. 1987;91:1204–13.
8. Garcia-Valenzuela E, Shareef S, Walsh J, Sharma SC. Programmed cell death of retinal ganglion cells during experimental glaucoma. Exp Eye Res. 1995;61:33–44.
9. Quigley HA, Nickells RW, Kerrigan LA, et al. Retinal ganglion cell death in experimental glaucoma and after axotomy occurs by apoptosis. Invest Ophthalmol Vis Sci. 1995;36:774–86.

10. Weber AJ, Kaufman PL, Hubbard WC. Morphology of single ganglion cells in the glaucomatous primate retina. Invest Ophthalmol Vis Sci. 1998;39: 2304–20.
11. Quigley HA, McKinnon SJ, Zack DJ, et al. Retrograde axonal transport of BDNF in retinal ganglion cells is blocked by acute IOP elevation in rats. Invest Ophthalmol Vis Sci. 2000;41:3460–6.
12. Quigley HA. Ganglion cell death in glaucoma: pathology recapitulates ontogeny. Aust N Z J Ophthalmol. 1995;23:85–91.
13. Wygnanski T, Desatnik H, Quigley HA, Glovinsky Y. Comparison of ganglion cell loss and cone loss in experimental glaucoma. Am J Ophthalmol. 1995; 120:184–9.
14. Panda S, Jonas JB. Decreased photoreceptor count in human eyes with secondary angle-closure glaucoma. Invest Ophthalmol Vis Sci. 1992;33:2532–6.
15. Kendell KR, Quigley HA, Kerrigan LA, Pease ME, Quigley EN. Primary open-angle glaucoma is not associated with photoreceptor loss. Invest Ophthalmol Vis Sci. 1995;36:200–5.
16. Nork TM, Ver Hoeve JN, Poulsen GL, et al. Swelling and loss of photoreceptors in chronic human and experimental glaucomas. Arch Ophthalmol. 2000; 118:235–45.
17. Janssen P, Naskar R, Moore S, Thanos S, Thiel HJ. Evidence for glaucoma-induced horizontal cell alterations in the human retina. Ger J Ophthalmol. 1996;5:378–85.
18. Yucel YH, Zhang Q, Gupta N, Kaufman PL, Weinreb RN. Loss of neurons in magnocellular and parvocellular layers of the lateral geniculate nucleus in glaucoma. Arch Ophthalmol. 2000;118:378–84.
19. Yucel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Atrophy of relay neurons in magno- and parvocellular layers in the lateral geniculate nucleus in experimental glaucoma. Invest Ophthalmol Vis Sci. 2001;42:3216–22.
20. Yucel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. Prog Retin Eye Res. 2003;22:465–81.
21. Gaasterland D, Tanishima T, Kuwabara T. Axoplasmic flow during chronic experimental glaucoma. 1. Light and electron microscopic studies of the monkey optic nervehead during development of glaucomatous cupping. Invest Ophthalmol Vis Sci. 1978;17:838–46.
22. Minckler DS, Bunt AH, Johanson GW. Orthograde and retrograde axoplasmic transport during acute ocular hypertension in the monkey. Invest Ophthalmol Vis Sci. 1977;16:426–41.
23. Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma. II. The site of injury and susceptibility to damage. Arch Ophthalmol. 1981;99:635–49.
24. Quigley HA, Green WR. The histology of human glaucoma cupping and optic nerve damage: clinicopathologic correlation in 21 eyes. Ophthalmology. 1979;86:1803–30.
25. Bellezza AJ, Rintalan CJ, Thompson HW, et al. Deformation of the lamina cribrosa and anterior scleral canal wall in early experimental glaucoma. Invest Ophthalmol Vis Sci. 2003;44:623–37.
26. Burgoyne CF, Downs JC, Bellezza AJ, Hart RT. Three-dimensional reconstruction of normal and early glaucoma monkey optic nerve head connective tissues. Invest Ophthalmol Vis Sci. 2004; 45:4388–99.
27. Downs JC, Suh JK, Thomas KA, et al. Viscoelastic material properties of the peripapillary sclera in normal and early-glaucoma monkey eyes. Invest Ophthalmol Vis Sci. 2005;46:540–6.
28. Downs JC, Yang H, Girkin C, et al. Three dimensional histomorphometry of the normal and early glaucomatous monkey optic nerve head: neural canal and subarachnoid space architecture. Invest Ophthalmol Vis Sci. 2007;48:3195–208.
29. Yang H, Downs JC, Girkin C, et al. 3-D histomorphometry of the normal and early glaucomatous monkey optic nerve head: lamina cribrosa and peripapillary scleral position and thickness. Invest Ophthalmol Vis Sci. 2007;48:4597–607.
30. Yang H, Downs JC, Bellezza AJ, Thompson H, Burgoyne CF. 3-D histomorphometry of the normal and early glaucomatous monkey optic nerve head: prelaminar neural tissues and cupping. Invest Ophthalmol Vis Sci. 2007;48:5068–84.
31. Johnson EC, Morrison JC, Farrell S, et al. The effect of chronically elevated intraocular pressure on the rat optic nerve head extracellular matrix. Exp Eye Res. 1996;62:663–74.
32. Johnson EC, Deppmeier LM, Wentzien SK, Hsu I, Morrison JC. Chronology of optic nerve head and retinal responses to elevated intraocular pressure. Invest Ophthalmol Vis Sci. 2000;41:431–42.
33. Cepurna WO, Kayton RJ, Johnson EC, Morrison JC. Age related optic nerve axonal loss in adult brown Norway rats. Exp Eye Res. 2005;80:877–84.
34. Howell GR, Libby RT, Jakobs TC, et al. Axons of retinal ganglion cells are insulted in the optic nerve early in DBA/2J glaucoma. J Cell Biol. 2007; 179:1523–37.
35. Anderson DR. Ultrastructure of human and monkey lamina cribrosa and optic nerve head. Arch Ophthalmol. 1969;82:800–14.
36. Morrison J, L'Hernault N, Jerdan J, Quigley H. Ultrastructural localization of extracellular matrix components in the monkey optic nerve head. Ubvest Iogtgaknik Vus Scu. 1988;29:353.
37. Quigley HA, Dorman-Pease ME, Brown AE. Quantitative study of collagen and elastin of the optic nerve head and sclera in human and experimental monkey glaucoma. Curr Eye Res. 1991;10:877–88.

38. Hernandez MR. Ultrastructural immunocytochemical analysis of elastin in the human lamina cribrosa. Changes in elastic fibers in primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 1992;33: 2891–903.
39. Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. Surv Ophthalmol. 1994;39:23–42.
40. Burgoyne CF, Morrison JC. The anatomy and pathophysiology of the optic nerve head in glaucoma. J Glaucoma. 2001;10:S16–8.
41. Burgoyne CF, Downs JC, Bellezza AJ, Suh JK, Hart RT. The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. Prog Retin Eye Res. 2005;24:39–73.
42. Bito LZ. Impact of intraocular pressure on venous outflow from the globe: a hypothesis regarding IOP-dependent vascular damage in normal-tension and hypertensive glaucoma. J Glaucoma. 1996;5: 127–34.
43. Langham M. The temporal relation between intraocular pressure and loss of vision in chronic simple glaucoma. Glaucoma. 1980;2:427–35.
44. Hayreh SS. Pathogenesis of cupping of the optic disc. Br J Ophthalmol. 1974;58:863–76.
45. Hayreh SS. Pathogenesis of optic nerve head changes in glaucoma. Semin Ophthalmol. 1986;1: 1–13.
46. Levkovitch-Verbin H, Quigley HA, Kerrigan-Baumrind LA, et al. Optic nerve transection in monkeys may result in secondary degeneration of retinal ganglion cells. Invest Ophthalmol Vis Sci. 2001;42:975–82.
47. Wax MB, Tezel G, Edward PD. Clinical and ocular histopathological findings in a patient with normal-pressure glaucoma. Arch Ophthalmol. 1998;116:993–1001.
48. Wax MB. Is there a role for the immune system in glaucomatous optic neuropathy? Curr Opin Ophthalmol. 2000;11:145–50.
49. Schwartz M. Lessons for glaucoma from other neurodegenerative diseases: can one treatment suit them all? J Glaucoma. 2005;14:321–3.
50. Schwartz M, Yoles E. Self-destructive and self-protective processes in the damaged optic nerve: implications for glaucoma. Invest Ophthalmol Vis Sci. 2000;41:349–51.
51. Anderson MG, Libby RT, Gould DB, Smith RS, John SW. High-dose radiation with bone marrow transfer prevents neurodegeneration in an inherited glaucoma. Proc Natl Acad Sci U S A. 2005;102: 4566–71.
52. Pederson JE, Anderson DR. The mode of progressive disc cupping in ocular hypertension and glaucoma. Arch Ophthalmol. 1980;98:490–5.
53. Pederson JE, Gaasterland DE. Laser-induced primate glaucoma. I. Progression of cupping. Arch Ophthalmol. 1984;102:1689–92.
54. Johns KJ, Leonard-Martin T, Feman SS. The effect of panretinal photocoagulation on optic nerve cupping. Ophthalmology. 1989;96:211–6.
55. Klein BE, Klein R, Lee KE, Hoyer CJ. Does the intraocular pressure effect on optic disc cupping differ by age? Trans Am Ophthalmol Soc. 2006;104: 143–8.
56. Sponsel WE, Shoemaker J, Trigo Y, et al. Frequency of sustained glaucomatous-type visual field loss and associated optic nerve cupping in Beaver Dam, Wisconsin. Clin Experiment Ophthalmol. 2001; 29:352–8.
57. Greenfield DS, Siatkowski RM, Glaser JS, Schatz NJ, Parrish 2nd RK. The cupped disc. Who needs neuroimaging? Ophthalmology. 1998;105:1866–74.
58. Bianchi-Marzoli S, Rizzo 3rd JF, Brancato R, Lessell S. Quantitative analysis of optic disc cupping in compressive optic neuropathy. Ophthalmology. 1995;102:436–40.
59. Schwartz JT, Reuling FH, Garrison RJ. Acquired cupping of the optic nerve head in normotensive eyes. Br J Ophthalmol. 1975;59:216–22.
60. Kalvin NH, Hamasaki DI, Gass JD. Experimental glaucoma in monkeys. I. Relationship between intraocular pressure and cupping of the optic disc and cavernous atrophy of the optic nerve. Arch Ophthalmol. 1966;76:82–93.
61. Vrabec F. Glaucomatous cupping of the human optic disk: a neuro-histologic study. Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1976;198:223–34.
62. Anderson DR, Cynader MS. Glaucomatous optic nerve cupping as an optic neuropathy. Clin Neurosci. 1997;4:274–8.
63. Quigley H, Anderson DR. Cupping of the optic disc in ischemic optic neuropathy. Trans Am Acad Ophthalmol Otolaryngol. 1977;83:755–62.
64. Trobe JD, Glaser JS, Cassady J, Herschler J, Anderson DR. Nonglaucomatous excavation of the optic disc. Arch Ophthalmol. 1980;98:1046–50.
65. Hayreh SS, Jonas JB. Optic disc morphology after arteritic anterior ischemic optic neuropathy. Ophthalmology. 2001;108:1586–94.
66. Hall ER, Klein BE, Knudtson MD, Meuer SM, Klein R. Age-related macular degeneration and optic disk cupping: the Beaver Dam Eye Study. Am J Ophthalmol. 2006;141:494–7.
67. Piette SD, Sergott RC. Pathological optic-disc cupping. Curr Opin Ophthalmol. 2006;17:1–6.
68. Alward WL. Macular degeneration and glaucoma-like optic nerve head cupping. Am J Ophthalmol. 2004;138:135–6.
69. Danesh-Meyer HV, Savino PJ, Sergott RC. The prevalence of cupping in end-stage arteritic and non-arteritic anterior ischemic optic neuropathy. Ophthalmology. 2001;108:593–8.
70. Ambati BK, Rizzo 3rd JF. Nonglaucomatous cupping of the optic disc. Int Ophthalmol Clin. 2001;41:139–49.
71. Greenfield DS. Glaucomatous versus nonglaucomatous optic disc cupping: clinical differentiation. Semin Ophthalmol. 1999;14:95–108.

72. Sharma M, Volpe NJ, Dreyer EB. Methanol-induced optic nerve cupping. Arch Ophthalmol. 1999;117:286.
73. Manor RS. Documented optic disc cupping in compressive optic neuropathy. Ophthalmology. 1995;102:1577–8.
74. Orgul S, Gass A, Flammer J. Optic disc cupping in arteritic anterior ischemic optic neuropathy. Ophthalmologica. 1994;208:336–8.
75. Sonty S, Schwartz B. Development of cupping and pallor in posterior ischemic optic neuropathy. Int Ophthalmol. 1983;6:213–20.
76. Votruba M, Thiselton D, Bhattacharya SS. Optic disc morphology of patients with OPA1 autosomal dominant optic atrophy. Br J Ophthalmol. 2003;87:48–53.
77. Quigley HA, Addicks EM. Chronic experimental glaucoma in primates. II. Effect of extended intraocular pressure elevation on optic nerve head and axonal transport. Invest Ophthalmol Vis Sci. 1980;19:137–52.
78. Hernandez MR. The optic nerve head in glaucoma: role of astrocytes in tissue remodeling. Prog Retin Eye Res. 2000;19:297–321.
79. Agapova OA, Kaufman PL, Lucarelli MJ, Gabelt BT, Hernandez MR. Differential expression of matrix metalloproteinases in monkey eyes with experimental glaucoma or optic nerve transection. Brain Res. 2003;967:132–43.
80. Johnson EC, Jia L, Cepurna WO, Doser TA, Morrison JC. Global changes in optic nerve head gene expression after exposure to elevated intraocular pressure in a rat glaucoma model. Invest Ophthalmol Vis Sci. 2007;48:3161–77.
81. Jonas JB, Dichtl A. Optic disc morphology in myopic primary open-angle glaucoma. Graefes Arch Clin Exp Ophthalmol. 1997;235:627–33.
82. Fernandez MC, Jonas JB, Naumann GO. Parapapillary chorioretinal atrophy in eyes with shallow glaucomatous optic disk cupping. Fortschr Ophthalmol. 1990;87:457–60.
83. Burgoyne CF, Downs JC. Optic nerve head (ONH) biomechanics underlies the clinical behaviour and susceptibility of the aged optic nerve head. J Glaucoma. 2008;17:318–28.
84. Rochtchina E, Mitchell P, Wang JJ. Relationship between age and intraocular pressure: the Blue Mountains Eye Study. Clin Experiment Ophthalmol. 2002;30:173–5.
85. Nomura H, Ando F, Niino N, Shimokata H, Miyake Y. The relationship between age and intraocular pressure in a Japanese population: the influence of central corneal thickness. Curr Eye Res. 2002; 24:81–5.
86. Nomura H, Shimokata H, Ando F, Miyake Y, Kuzuya F. Age-related changes in intraocular pressure in a large Japanese population: a cross-sectional and longitudinal study. Ophthalmology. 1999;106:2016–22.
87. Klein BE, Klein R, Linton KL. Intraocular pressure in an American community. The Beaver Dam Eye Study. Invest Ophthalmol Vis Sci. 1992;33:2224–8.
88. Weih LM, Mukesh BN, McCarty CA, Taylor HR. Association of demographic, familial, medical, and ocular factors with intraocular pressure. Arch Ophthalmol. 2001;119:875–80.
89. Leske MC, Connell AM, Wu SY, Hyman L, Schachat AP. Distribution of intraocular pressure. The Barbados Eye Study. Arch Ophthalmol. 1997;115: 1051–7.
90. Wu SY, Leske MC. Associations with intraocular pressure in the Barbados Eye Study. Arch Ophthalmol. 1997;115:1572–6.
91. Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. J Am Med Assoc. 1991;266:369–74.
92. Suzuki Y, Iwase A, Araie M, et al. Risk factors for open-angle glaucoma in a Japanese population: the Tajimi Study. Ophthalmology. 2006;113: 1613–7.
93. Friedman DS, Jampel HD, Munoz B, West SK. The prevalence of open-angle glaucoma among blacks and whites 73 years and older: the Salisbury Eye Evaluation Glaucoma Study. Arch Ophthalmol. 2006;124:1625–30.
94. Chumbley LC, Brubaker RF. Low-tension glaucoma. Am J Ophthalmol. 1976;81:761–7.
95. Drance SM, Sweeney VP, Morgan RW, Feldman F. Studies of factors involved in the production of low tension glaucoma. Arch Ophthalmol. 1973;89:457–65.
96. Goldberg I, Hollows FC, Kass MA, Becker B. Systemic factors in patients with low-tension glaucoma. Br J Ophthalmol. 1981;65:56–62.
97. Klein BE, Klein R, Sponsel WE, et al. Prevalence of glaucoma. The Beaver Dam Eye Study. Ophthalmology. 1992;99:1499–504.
98. Levene RZ. Low tension glaucoma: a critical review and new material. Surv Ophthalmol. 1980;24: 621–64.
99. Shiose Y. Prevalence and clinical aspects of low-tension glaucoma. Philadelphia: Lippincott; 1983.
100. Geijssen HC. Studies on normal pressure glaucoma. Amstelveen: Kugler; 1991.
101. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:714–20; discussion 829–730.
102. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627–35.
103. Heijl A, Leske MC, Bengtsson B, Hussein M. Measuring visual field progression in the Early Manifest Glaucoma Trial. Acta Ophthalmol Scand. 2003;81:286–93.
104. Greene PR. Mechanical considerations in myopia: relative effects of accommodation, convergence, intraocular pressure, and the extraocular muscles. Am J Optom Physiol Opt. 1980;57:902–14.

105. Bellezza AJ, Hart RT, Burgoyne CF. The optic nerve head as a biomechanical structure: initial finite element modeling. Invest Ophthalmol Vis Sci. 2000;41:2991–3000.
106. Sigal IA, Flanagan JG, Ethier CR. Factors influencing optic nerve head biomechanics. Invest Ophthalmol Vis Sci. 2005;46:4189–99.
107. Sigal IA, Flanagan JG, Tertinegg I, Ethier CR. Reconstruction of human optic nerve heads for finite element modeling. Technol Health Care. 2005;13:313–29.
108. Sigal IA, Flanagan JG, Tertinegg I, Ethier CR. Finite element modeling of optic nerve head biomechanics. Invest Ophthalmol Vis Sci. 2004;45:4378–87.
109. Repka MX, Quigley HA. The effect of age on normal human optic nerve fiber number and diameter. Ophthalmology. 1989;96:26–32.
110. Balazsi AG, Rootman J, Drance SM, Schulzer M, Douglas GR. The effect of age on the nerve fiber population of the human optic nerve. Am J Ophthalmol. 1984;97:760–6.
111. Morrison JC, Cork LC, Dunkelberger GR, Brown A, Quigley HA. Aging changes of the rhesus monkey optic nerve. Invest Ophthalmol Vis Sci. 1990; 31:1623–7.
112. Cull G, Cioffi GA, Dong J, Homer L, Wang L. Estimating normal optic nerve axon numbers in non-human primate eyes. J Glaucoma. 2003;12: 301–6.
113. Sandell JH, Peters A. Effects of age on the glial cells in the rhesus monkey optic nerve. J Comp Neurol. 2002;445:13–28.
114. Sandell JH, Peters A. Effects of age on nerve fibers in the rhesus monkey optic nerve. J Comp Neurol. 2001;429:541–53.
115. Frisen L. High-pass resolution perimetry and age-related loss of visual pathway neurons. Acta Ophthalmol (Copenh). 1991;69:511–5.
116. Albon J, Purslow PP, Karwatowski WS, Easty DL. Age related compliance of the lamina cribrosa in human eyes. Br J Ophthalmol. 2000;84:318–23.
117. Morrison JC, Jerdan JA, Dorman ME, Quigley HA. Structural proteins of the neonatal and adult lamina cribrosa. Arch Ophthalmol. 1989;107: 1220–4.
118. Pena JD, Roy S, Hernandez MR. Tropoelastin gene expression in optic nerve heads of normal and glaucomatous subjects. Matrix Biol. 1996;15:323–30.
119. Quigley HA. Childhood glaucoma: results with trabeculotomy and study of reversible cupping. Ophthalmology. 1982;89:219–26.
120. Hernandez MR, Luo XX, Andrzejewska W, Neufeld AH. Age-related changes in the extracellular matrix of the human optic nerve head. Am J Ophthalmol. 1989;107:476–84.
121. Jeffery G, Evans A, Albon J, et al. The human optic nerve: fascicular organisation and connective tissue types along the extra-fascicular matrix. Anat Embryol (Berl). 1995;191:491–502.
122. Albon J, Karwatowski WS, Easty DL, Sims TJ, Duance VC. Age related changes in the non-collagenous components of the extracellular matrix of the human lamina cribrosa. Br J Ophthalmol. 2000;84:311–7.
123. Bailey AJ, Paul RG, Knott L. Mechanisms of maturation and ageing of collagen. Mech Ageing Dev. 1998;106:1–56.
124. Brown CT, Vural M, Johnson M, Trinkaus-Randall V. Age-related changes of scleral hydration and sulfated glycosaminoglycans. Mech Ageing Dev. 1994;77:97–107.
125. Albon J, Karwatowski WS, Avery N, Easty DL, Duance VC. Changes in the collagenous matrix of the aging human lamina cribrosa. Br J Ophthalmol. 1995;79:368–75.
126. Friedenwald J. It is evident that an increasing rigidity of the ocular coats is characteristic of advancing age. AJO. 1937;20:985–1024.
127. Kotecha A, Izadi S, Jeffrey G. Age related changes in the thickness of the human lamina cribrosa. Br J Ophthalmol. 2006;90:1531–4.
128. Albon J, Farrant S, Akhtar S, et al. Connective tissue structure of the tree shrew optic nerve and associated ageing changes. Invest Ophthalmol Vis Sci. 2007;48:2134–44.
129. Grunwald JE, Piltz J, Patel N, Bose S, Riva CE. Effect of aging on retinal macular microcirculation: a blue field simulation study. Invest Ophthalmol Vis Sci. 1993;34:3609–13.
130. Harris A, Harris M, Biller J, et al. Aging affects the retrobulbar circulation differently in women and men. Arch Ophthalmol. 2000;118:1076–80.
131. Hernandez MR, Wang N, Hanley NM, Neufeld AH. Localization of collagen types I and IV mRNAs in human optic nerve head by in situ hybridization. Invest Ophthalmol Vis Sci. 1991;32: 2169–77.
132. May CA. The optic nerve head region of the aged rat: an immunohistochemical investigation. Curr Eye Res. 2003;26:347–54.
133. Investigators TA. The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130:429–40.
134. Kass MA, Heuer DK, Higginbotham EJM, et al. The ocular hypertension treatment study (a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma). Arch Ophthalmol. 2002;120: 701–13.
135. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121:48–56.
136. Anderson DR, Drance SM, Schulzer M. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. Am J Ophthalmol. 2003;136:820–9.

137. Zeimer R. Could glaucoma damage be due to a viscoelastic mismatch between the sclera and the lamina cribrosa? J Jpn Glaucoma Soc. 1992;2:17–20.
138. Zeimer R. Biomechanical properties of the optic nerve head. In: Drance SM, editor. Optic nerve in glaucoma. Amsterdam: Kugler; 1995. p. 107–21.
139. Jonas JB, Berenshtein E, Holbach L. Lamina cribrosa thickness and spatial relationships between intraocular space and cerebrospinal fluid space in highly myopic eyes. Invest Ophthalmol Vis Sci. 2004;45:2660–5.
140. Cioffi GA, Van Buskirk EM. Vasculature of the anterior optic nerve and peripapillary choroid. 2nd ed. St. Louis: Mosby; 1996. p. 177–97.
141. Quigley HA. Overview and introduction to session on connective tissue of the optic nerve in glaucoma. Chapter 2. In: Drance SM, Anderson DR, editors. Optic nerve in glaucoma. Amsterdam: Kugler Publications; 1995. p. 15–36.
142. Morrision JC, L'Hemault NL, Jerdan JA, Quigley HA. Ultrastructural location of extracellular matrix components in the optic nerve head. Arch Opthamol. 1989;107:123–9.
143. Emery JM, Landis D, Paton D, Boniuk M, Craig JM. The lamina cribrosa in normal and glaucomatous human eyes. Trans Am Acad Ophthalmol Otolaryngol. 1974;78:OP290–7.
144. Quigley HA, Hohman RM, Addicks EM, Massof RW, Green WR. Morphologic changes in the lamina cribrosa correlated with neural loss in open-angle glaucoma. Am J Ophthalmol. 1983;95:673–91.

Optic Nerve: Clinical Examination

2

Marcelo T. Nicolela and Jayme R. Vianna

Core Messages

- Optic disc evaluation is of fundamental importance in the management of glaucoma.
- Clinical examination of the optic disc is best performed with slit lamp biomicroscopy, utilizing contact or handheld lenses.
- Subjective assessment or measurement of optic disc size is paramount, as there is a strong correlation between optic disc size and optic cup size.
- Great attention should be paid to neuroretinal rim contour, as well as the presence of retinal nerve fiber layer defects and optic disc hemorrhages, which can easily be missed.
- Over time, disc changes are better identified with optic disc photographs or automated devices. The rate of disc changes in glaucoma is quite variable in different individuals and depends upon the stage of the disease, among other things.
- A large proportion of individuals with optic disc hemorrhages will present with progressive changes in the optic nerve fiber layer or optic disc within 2 years of hemorrhage, and these individuals should be monitored closely.

2.1 How Should I Examine the Optic Nerve?

Optic nerve-head examination is probably the most important step in the diagnosis of glaucoma and is also extremely important in monitoring patients with established glaucoma. There are several ways to clinically examine the optic nerve head, including direct ophthalmoscopy, indirect ophthalmoscopy, and slit lamp biomicroscopy with contact lenses (such as a Goldman lens), handheld lenses (such as a 78- or 90-diopter lens), or the Hruby lens. The advantages of slit lamp biomicroscopy, the preferred method for optic nerve evaluation, over the other methods mentioned are the quality of the stereopsis and magnification provided. Although slit lamp biomicroscopy with handheld lenses can be performed through an undilated pupil, a stereoscopic view may be possible only if the pupil is dilated.

In addition to slit lamp examination, optic disc stereophotography provides complimentary clinical information. For example, data from the

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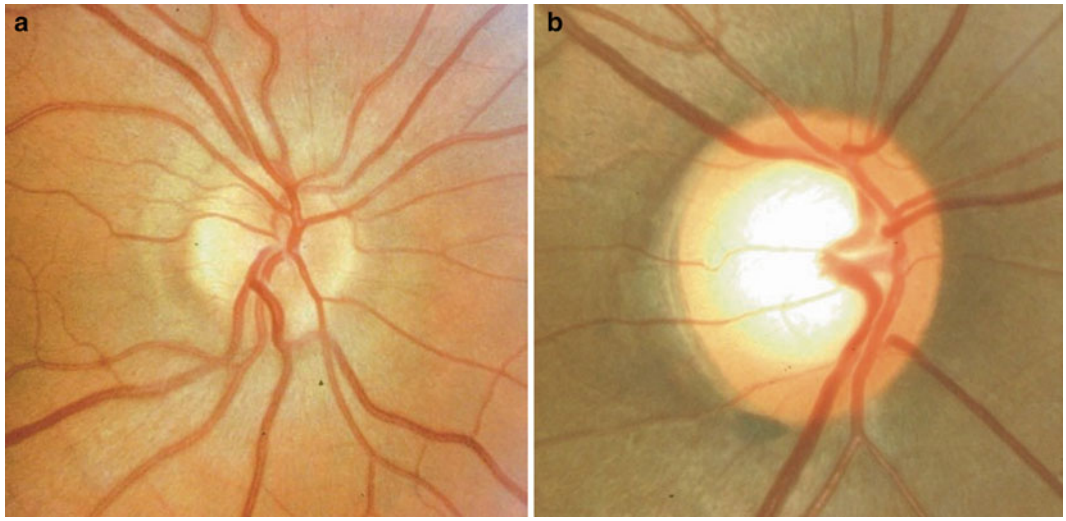

Fig. 2.1 Examples of a small optic disc (**a**) and a large optic disc (**b**). The disc and rim areas, measured with confocal scanning laser tomography, were 1.3 and 1.1 mm^2 in disc (**a**) and 3.5 and 1.6 mm^2 in disc (**b**). Note that the whole disc of example (**a**) is smaller than just the rim area alone in example (**b**)

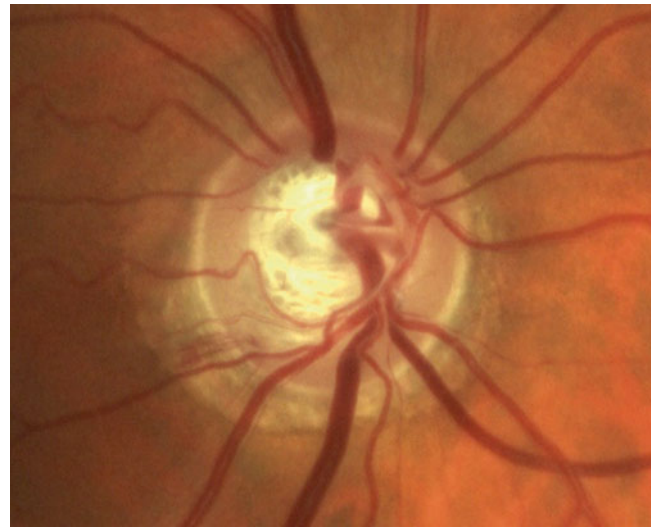

Fig. 2.2 Optic disc with infero-temporal disc hemorrhage, associated with thinning of the neuroretinal rim in the same location. The inferior circumlinear blood vessels exhibit baring

Ocular Hypertension Treatment Study (OHTS) show that 84 % of 128 cases of optic disc hemorrhages were detected on disc photographs but not on the clinical exam [1].

Clinical examination of the optic nerve should be performed with similar methodology each and every time it is executed, in order not to miss important aspects of the examination. In my view, examination of the optic nerve head should start with an evaluation of optic disc size since disc size is extremely important in the interpretation of other optic nerve findings (see Fig. 2.1). Even a simple subjective assessment, without specific measurements, of whether the disc is small, large, or average in size can be of value. The exam should then proceed to a careful assessment of the neuroretinal rim, looking for areas of thinning, notching, nasal cupping, and vessel abnormalities. There is a helpful rule for examining the contour of the neuroretinal rim (the ISNT mnemonic), which states that in normal discs the inferior neuroretinal rim is thickest, followed in

decreasing order by the superior, nasal, and temporal neuroretinal rims [2, 3]. The optic nerve in Fig. 2.1b follows the ISNT rule, while the nerve in Fig. 2.2 does not. After the disc size is estimated and the neuroretinal rim has been examined, one should examine the peripapillary area carefully, paying great attention to the presence of optic disc hemorrhages and retinal nerve fiber layer defects (both diffuse and localized), and, to a lesser degree, to the presence and location of peripapillary atrophy [4–9].

Summary for the Clinician

- Examination of the optic nerve is critical for the diagnosis of glaucoma and its progression.
- Slit lamp biomicroscopy with handheld lenses is the best method of optic nerve examination since it provides good stereopsis and magnification.
- Optic disc stereophotographs are complementary to slit lamp examination and may pick up findings missed on the clinical exam.
- Optic nerve examination should be systematic.
- Disc size (small, average, large) should be estimated first.
- The neuroretinal rim should be examined for diffuse and focal changes. The ISNT rule is helpful.
- Disc hemorrhages, nerve fiber layer defects, and peripapillary atrophy should also be noted.

2.2 How Does One Establish the Borders of the Nerve and Follow the Neuroretinal Rim Contour?

In clinical studies, the disc margin is determined as the internal edge of the scleral ring. In most cases, identification of the white scleral ring is relatively easy although it might not be clearly visible all the way around the optic disc, especially in the nasal area (Fig. 2.3). Establishing the borders of the optic nerve can be very challenging in cases of tilted discs, crowded discs, or highly myopic eyes with significant peripapillary atrophy.

The neuroretinal rim is identified by its normally pink color and/or the change of contour from the rim to the cup, which is best determined

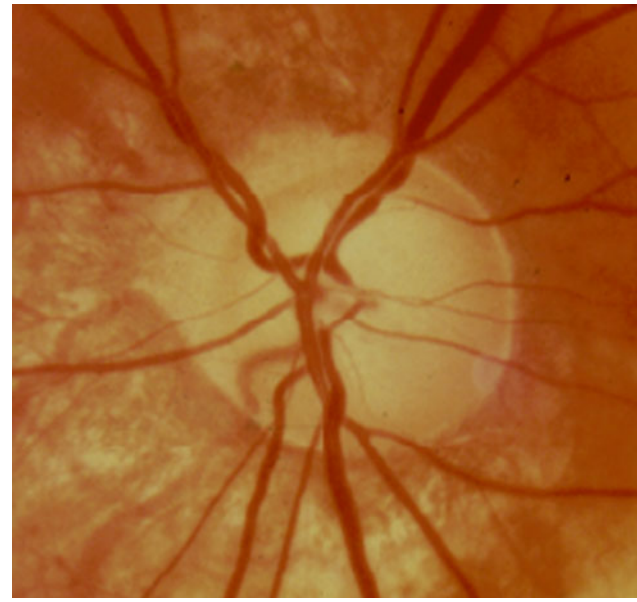

Fig. 2.3 Example of an optic disc with a sclerotic appearance. The internal borders of the neuroretinal rim are usually difficult to determine in these discs with a saucerized type of cupping

by following the trajectory of the blood vessels within the optic disc. Determining and describing the internal borders of the neuroretinal rim (or the limits of its excavation) is sometimes difficult. The size of the optic cup varies significantly in normal eyes, and it is strongly correlated with the size of optic disc [3]. Normally, circumlinear blood vessels rest on neuroretinal rim. Therefore, in most cases, the boundaries of the optic disc cup are best determined by following the trajectory of these vessels inside the optic disc. As neuroretinal rim disappears underneath the blood vessels, various terms are used to describe the appearance of the unsupported blood vessels. "Bayonetting," a term borrowed from the shape of bayonet guns, refers to the sharp 90° turn (or occasionally more than 90° turn) a blood vessel develops as it dips into an acquired pit of neuroretinal rim loss and then emerges out onto the disc edge (see Fig. 2.2). "Baring" of circumlinear vessels refers to the unsupported appearance vessels have when there is no neuroretinal rim directly in contact with them (see Fig. 2.2). "Nasalization" of blood vessels occurs as increased cupping causes a nasal shift of the major blood vessels emerging from the nerve. Blood vessels can also narrow as glaucoma develops. In the so-called sloped or saucerized cups, oftentimes present in sclerotic optic discs, the precise determination of the borders of the cup is more difficult and subjective, and a good stereoscopic view of the optic nerve is extremely helpful in those situations (Fig. 2.3) [10].

Recent studies with Spectral Domain OCT (SDOCT) provide new insights on the anatomy of the optic disc head. Reis et al. [11] have shown that the clinically defined disc margin does not have one unique anatomic correlate on OCT images, but might rather co-localize to the ending of Bruch's membrane or other aspects of the border tissue of Elschnig, which varies between individuals and between regions of a single eye. In addition, the geometrical orientation used to measure the neuroretinal rim has been evaluated and a new minimum rim width presented better diagnostic ability than the traditional horizontal plane following the back of the eye [12]. Figure 2.4 illustrates how information from SDOCT can be incorporated into the clinical evaluation of a suspect optic disc.

Summary for the Clinician

- Correctly identify the edge of the disc/scleral ring as the first step of evaluation.
- Follow the trajectory of the vessels on the optic disc to assess the contour of the neuroretinal rim. Look for bayoneting, baring, nasalization, and narrowing of the blood vessels.
- New analysis of optic disc OCT might complement the clinical examination.

2.3 How Does One Avoid Misinterpreting Rim Loss?

The inherent variability in size and shape of the optic disc among normal individuals and among patients with glaucoma hampers the clinician's ability to determine rim loss with high accuracy. Detection of rim loss over time can have higher specificity than cross-sectional detection of glaucoma, since detection over time does not depend on the interindividual variability of optic disc appearance. Nevertheless, certain steps should be taken to avoid misinterpreting rim loss.

The first step for a correct interpretation of rim loss is factoring in the assessment of optic disc size, as mentioned earlier. Optic disc size can influence the interpretation of rim loss in two ways: (1) a large optic disc might appear to be glaucomatous because large discs normally have large cups and apparently thin neuroretinal rim, although if one measures the total area of the neuroretinal rim it is usually larger in large discs; (2) a small optic disc might "hide" neuroretinal rim loss, as sometimes even a small cup in a small disc is abnormal (Fig. 2.1) Another step to avoid misinterpretation of rim loss is careful observation of rim contour as opposed to cup size, which can lead one to miss subtle changes of the neuroretinal rim. Looking for matching clues between the inside and outside of the optic disc is also useful, such as confirming the presence of an RNFL defect or hemorrhage in an area where the neuroretinal rim is suspicious.

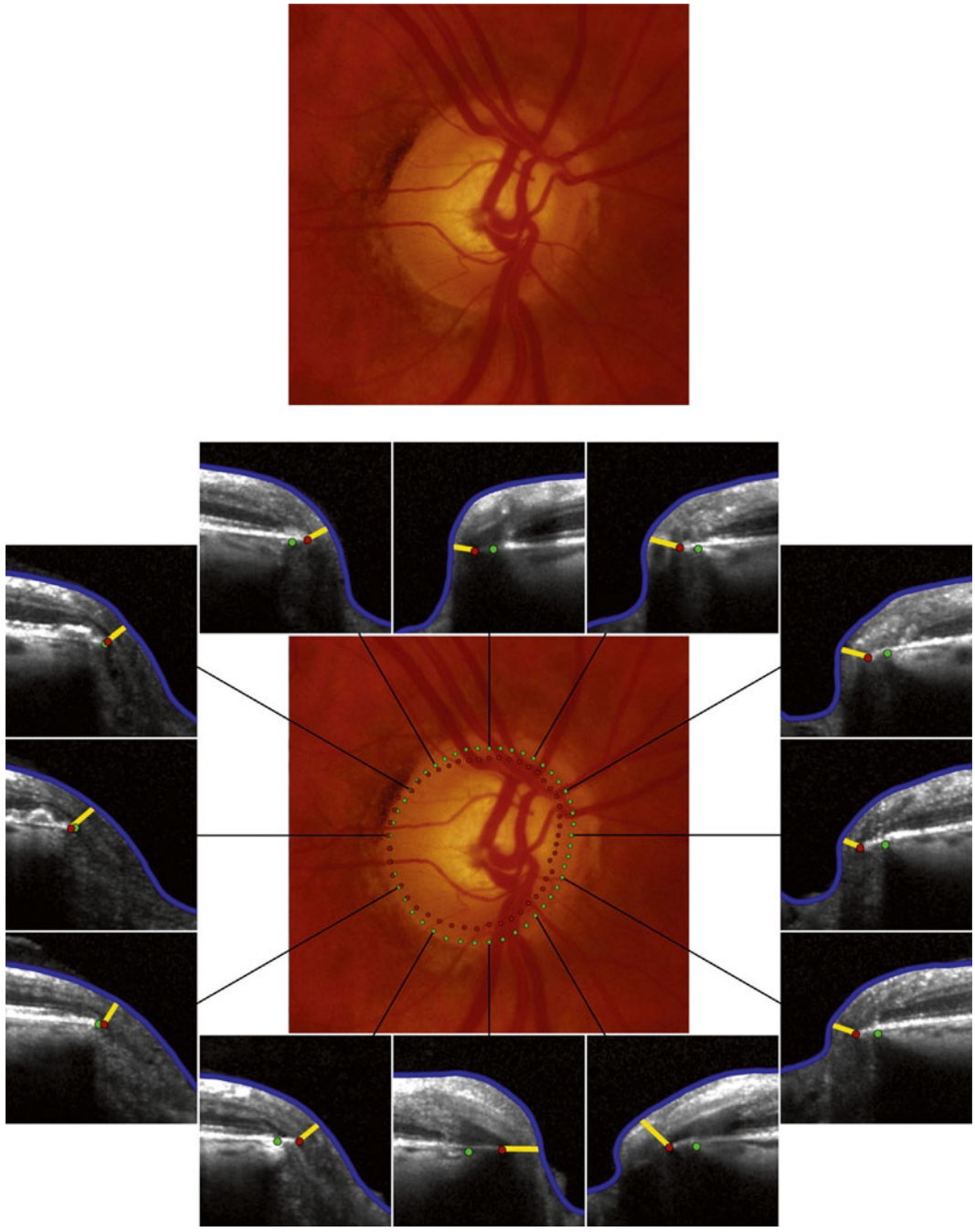

Fig. 2.4 Example of spectral-domain optical coherence tomography (SD OCT) evaluation of a right eye suspected of glaucoma (*Top* photo). In this case, SD OCT with analysis of Bruch's membrane opening minimum rim width (BMO-MRW) by clock hour (*Bottom*) provides valuable additional information. There is a considerable mismatch between the clinically visible disc margin (*green dots*) and BMO (*red dots*), indicating an invisible extension of Bruch's membrane inside the clinically determined disc margin, particularly inferiorly and nasally (note the mismatch between the red and green dots in the three inferior OCT scans). In these locations, as well as in the superior sector, which is the most suspicious, the neuroretinal rim is considerably thinner than the clinician would estimate from a disc margin-based evaluation (reproduced with license from [13] © Elsevier)

The color of the rim should also be evaluated. Even though some non-glaucomatous optic neuropathy may show optic disc cupping, a mismatch between the amount of pallor and the rim loss increases the likelihood that a non-glaucomatous optic neuropathy is present [14].

One should acknowledge that interpretation of optic disc findings is subjective and agreement is less than perfect, even among fellowship-trained glaucoma subspecialists. Most studies report only moderate agreement among specialists in detecting glaucomatous abnormality [15, 16]. Similarly, agreement in determining progressive rim loss from serial optic disc photographs has been less than ideal, with most studies showing moderate agreement [17–20]. The Glaucomatous Optic Neuropathy Evaluation Project (gone-project.com) is an interesting free online tool to exercise optic disc evaluation [21].

Summary for the Clinician

- Pay attention to rim contour rather than to cup size.
- Pay attention to disc size, as it affects the apparent amount of neuroretinal rim.
- Pay attention to rim color.
- Look for corroborating findings between the rim and the nerve fiber layer.
- Acknowledge that interpretation of optic disc findings is subjective. Agreement is not perfect even among experienced fellowship-trained glaucoma specialists.

2.4 How Much Asymmetry Between Neuroretinal Rims and Nerves Is Important?

Cup to disc ratio asymmetry of 0.2 or greater has long been held to be suggestive of glaucoma. In a variety of research studies, the definition of a glaucomatous optic disc has included asymmetry of 0.2 or greater between fellow eyes [22]. However, data from the Blue Mountains population study showed that cup to disc asymmetry is significantly associated with optic disc size asymmetry and that asymmetry alone was not useful in identifying patients with glaucoma (in fact, at all levels of asymmetry [0.2, 0.3, 0.4, etc.] individuals were more likely to be normal than to have glaucoma) [23]. Therefore, when assessing asymmetry of cup or neuroretinal rim between eyes it is important to examine whether or not the optic disc size and shape are symmetrical. It is also advisable to correlate the asymmetric disc findings with other findings such as intraocular pressure (IOP) asymmetry or visual field asymmetry, even very subtle asymmetry. In our experience, the vast majority of cases referred to me as glaucoma suspects solely on the basis of optic disc cup asymmetry, without other significant findings suggestive of glaucoma, turn out to have optic disc size asymmetry accounting for the cup asymmetry.

Summary for the Clinician

- Cup to disc ratio asymmetry of 0.2 or greater is part of the classic definition of glaucoma.
- Asymmetry of optic disc size and shape can give the appearance of cup to disc ratio asymmetry.
- Asymmetry of cup to disc ratios should be correlated to asymmetry in other parts of the clinical examination (i.e., IOP, visual field sensitivity, quantitative measurements of the optic nerve or RNFL).

2.5 How Can I Estimate Disc Size and Compare Disc Size Between the Two Eyes?

Disc size can be estimated by a variety of methods. During clinical examination, disc size can be estimated with the direct ophthalmoscope in a technique described by Gross. The 5° aperture of the Welch-Allyn ophthalmoscope produces a

circular spot with a diameter of 1.5 mm and an area of 1.77 mm^2, which is slightly smaller than an average-sized optic disc, which has an approximate area of 2.1–2.7 mm^2 [24]. Another option, which is easier in our opinion, is to adjust the height of the slit lamp beam to coincide with the edges of the optic disc while performing biomicroscopy with handheld lenses such as the 90-diopter or contact lenses. The height of the slit beam can then be read off the scale [25, 26]. Disc size comparisons between eyes can easily be done with either one of the methods described above.

The use of automated optic disc technology, such as confocal scanning laser tomography (clinical instrument is the Heidelberg retinal tomograph—HRT), also allows for a fairly accurate, easy assessment of optic disc size and comparisons between the two eyes, however the contour line has to be correctly marked.

Summary for the Clinician

- The 5° aperture on the direct Welch-Allyn ophthalmoscope is just slightly smaller than an average-sized optic nerve head and can be used to approximate optic nerve-head size.
- During slit lamp biomicroscopy with a handheld lens, the slit beam can be adjusted to measure the height of the optic nerve heads.
- Optic nerve-head size can be easily measured with confocal scanning laser tomography.

2.6 How Can I Look for Optic Nerve Change Over Time?

The rate of optic nerve change, similar to the rate of visual field change, is extremely variable among different patients, even in patients with similar IOP levels. It is always difficult to define rates of change because of the generally slow nature of the disease (which means studies require very long follow-up time), the lack of universally accepted methods to assess change (different criteria will lead to different "rates of progression"), and the fact that we cannot pinpoint the "beginning of the glaucomatous process" (therefore, any given study will contain individuals who are in different stages of their disease and probably are already undergoing change) [27].

Methods to assess change of the optic disc over time include the use of optic disc drawing comparisons, sequential optic disc photographs (mono or stereo), and quantitative and qualitative parameters on automated devices, such as confocal scanning ophthalmoscopy. In our opinion, subjective drawings are not very useful, and therefore, disc photographs or automated devices are the best options in assessing structural change in glaucoma.

Optic disc changes are more easily observed in early cases of glaucoma when the dynamic range for change is greater. In more advanced cases, the optic disc may be too damaged to appreciably note further thinning of the neuroretinal rim, and at this point in the disease it is easier to follow progression of the visual field. Data from randomized clinical trials of ocular hypertensive individuals has provided information regarding rate of optic disc change in these individuals. In the observation group of the OHTS, the cumulative probability of conversion to glaucoma over 60 months was 9.5 and 67 % of these individuals converted to glaucoma on the basis of optic disc change alone. In the European Glaucoma Prevention Study (EGPS), the cumulative probability of conversion to glaucoma in the placebo group after 60 months was 14 %, but only 37 % of the conversions occurred on the basis of optic disc changes [28]. The difference in optic disc progression rate between the OHTS and the EGPS highlights how different criteria can lead to different progression rates.

Possible glaucomatous changes over time that can occur on the optic disc include diffuse or focal thinning of the neuroretinal rim, widening or appearing of a retinal nerve fiber layer defect, and enlargement of beta-zone peripapillary atrophy. In addition to that, detection of a new optic

disc hemorrhage is a significant finding, probably the most significant predictor of visual field progression [29].

Summary for the Clinician

- The rate of optic nerve change is variable from one individual to the next.
- There are many barriers to detecting optic nerve change.
- Probably the best way(s) to monitor for optic nerve change is to use photo documentation and/or automated devices.
- Changes in the optic nerve are more easily detected when significant rim is available to observe the change.

2.7 If I See a Disc Hemorrhage on Healthy Appearing Neuroretinal Rim, How Soon Can I Expect to See a Change in the Rim?

In the OHTS, progressive changes occurred in only 14 % of patients with ocular hypertension who had at least one disc hemorrhage [1]. Data from the Blue Mountain study also have shown that despite a strong association between the presence of optic disc hemorrhage and established glaucoma (with visual field defect), the majority of disc hemorrhages (70 %) were found in individuals without definite signs of glaucoma [30]. Unfortunately, very few studies to date have reported on the follow-up of these "normal" individuals with disc hemorrhages. In repeated glaucoma surveys performed in the population of Dalby, disc hemorrhages were found in 28 out of 3819 individuals without glaucoma (prevalence of 0.7 %). Five out of ten of these individuals who were followed developed glaucoma with a visual field defect 2–7 years after the disc hemorrhage was noted [31].

A more common situation is the occurrence of a disc hemorrhage on a healthy appearing area of the neuroretinal rim in a glaucomatous disc. Disc hemorrhages usually occur at the infero-temporal or supero-temporal areas of the rim. Often they recur in the same area until a notch is formed, and then will start occurring at the opposite side of the same disc where the rim is still normal [6, 32–34]. Studies have shown that optic disc progression occurs in 50–80 % of patients with glaucoma following an optic disc hemorrhage, with median follow-up of 2–3 years [1, 35, 36].

Besides being a risk factor for future visual field progression, disc hemorrhages were detected more frequently on locations corresponding to the visual field sector with fastest pre-hemorrhage progression rates [37], suggesting that the hemorrhages are indicators of active ongoing glaucomatous damage. Therefore, it is important for the clinician to carefully monitor glaucoma patients after optic disc hemorrhages.

Summary for the Clinician

- Disc hemorrhages occur in non-glaucomatous eyes.
- In initially non-glaucomatous eyes, it is unclear what percent of nerves and over what period of time glaucomatous change of the optic nerve occurs after disc hemorrhage. One study found a visual field defect to occur after 2–7 years in 5 of 10 eyes that were followed.
- In optic nerves with established glaucoma, disc hemorrhages are more common.
- Disc hemorrhages are typically found in the infero-temporal or supero-temporal regions of the optic nerve.
- 50–80 % of patients with glaucoma and disc hemorrhages have been found to progress after 2–3 years of follow-up.
- 14 % of patients in the OHTS study with disc hemorrhages showed progressive neuroretinal rim loss after median follow-up of 13 months.

References

1. Budenz DL, Anderson DR, Feuer WJ, Beiser JA, Schiffman J, Parrish RK, et al. Detection and prognostic significance of optic disc hemorrhages during the ocular hypertension treatment study. Ophthalmology. 2006;113:2137–43.
2. Jonas JB, Gusek GC, Naumann GOH. Optic disc morphometry in chronic primary open-angle glaucoma—I. Morphometric intrapapillary characteristics. Graefes Arch Clin Exp Ophthalmol. 1988;226:522–30.
3. Jonas JB, Gusek GC, Naumann GOH. Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. Invest Ophthalmol Vis Sci. 1988;29:1151–8.
4. Airaksinen PJ, Heijl A. Visual field and retinal nerve fibre layer in early glaucoma after optic disc haemorrhage. Acta Ophthalmol. 1983;61:186–94.
5. Airaksinen PJ, Tuulonen A, Werner EB. Clinical evaluation of the optic disc and retinal nerve fiber layer. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas. St. Louis: Mosby; 1996. p. 617–57.
6. Drance SM. Disc hemorrhages in the glaucomas. Surv Ophthalmol. 1989;33:331–7.
7. Jonas JB, Nguyen XN, Gusek GC, Naumann GOH. Parapapillary chorioretinal atrophy in normal and glaucoma eyes. I. Morphometric data. Invest Ophthalmol Vis Sci. 1989;30:908–18.
8. Jonas JB, Schiro D. Localised wedge shaped defects of the retinal nerve fibre layer in glaucoma. Br J Ophthalmol. 1994;78:285–90.
9. Sommer A, Katz J, Quigley HA, Miller NR, Robin AL, Richter RC, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. Arch Ophthalmol. 1991;109:77–83.
10. Nicolela MT, Drance SM. Various glaucomatous optic nerve appearances: clinical correlations. Ophthalmology. 1996;103:640–9.
11. Reis ASC, Sharpe GP, Yang H, Nicolela MT, Burgoyne CF, Chauhan BC. Optic disc margin anatomy in patients with glaucoma and normal controls with spectral domain optical coherence tomography. Ophthalmology. 2012;119(4):738–47.
12. Chauhan BC, O'Leary N, Almobarak FA, Reis ASC, Yang H, Sharpe GP, et al. Enhanced detection of open-angle glaucoma with an anatomically accurate optical coherence tomography-derived neuroretinal rim parameter. Ophthalmology. 2013;120(3):535–43.
13. Chauhan BC, Burgoyne CF. From clinical examination of the optic disc to clinical assessment of the optic nerve head: a paradigm change. Am J Ophthalmol. 2013;156(2):218–27.e2.
14. Greenfield DS, Siatkowski RM, Glaser JS, Schatz NJ, Parrish RK. The cupped disc. Who needs neuroimaging? Ophthalmology. 1998;105(10):1866–74.
15. Abrams LS, Scott IU, Spaeth GL, Quigley HA, Varma R. Agreement among optometrists, ophthalmologists, and residents in evaluating the optic disc for glaucoma. Ophthalmology. 1994;101:1662–7.
16. Varma R, Steinmann WC, Scott IU. Expert agreement in evaluating the optic disc for glaucoma. Ophthalmology. 1992;99:215–21.
17. Azuara-Blanco A, Katz LJ, Spaeth GL, Vernon SA, Spencer F, Lanzl IM. Clinical agreement among glaucoma experts in the detection of glaucomatous changes of the optic disk using simultaneous stereoscopic photographs. Am J Ophthalmol. 2003;136:949–50.
18. Coleman AL, Sommer A, Enger C, Knopf HL, Stamper RL, Minckler DS. Interobserver and intraobserver variability in the detection of glaucomatous progression of the optic disc. J Glaucoma. 1996;5:384–9.
19. Ervin JC, Lemij HG, Mills RP, Quigley HA, Thompson HW, Burgoyne CF. Clinician change detection viewing longitudinal stereophotographs compared to confocal scanning laser tomography in the LSU Experimental Glaucoma (LEG) study. Ophthalmology. 2002;109:467–81.
20. Zeyen T, Miglior S, Pfeiffer N, Cunha-Vaz J, Adamsons I. Reproducibility of evaluation of optic disc change for glaucoma with stereo optic disc photographs. Ophthalmology. 2003;110:340–4.
21. Kong G, O'Neill E, Gurria L, Coote M, Crowston J. GONE Project [Internet]. 2008. http://www.gone-project.com. Accessed 2 Feb 2015
22. Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE, de Jong PT. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. Ophthalmology. 1994;101:1851–5.
23. Ong LS, Mitchell P, Healey PR, Cumming RG. Asymmetry in optic disc parameters: The blue mountains eye study. Invest Ophthalmol Vis Sci. 1999;40:849–57.
24. Gross PG, Drance SM. Comparison of a simple ophthalmoscopic and planimetric measurement of glaucomatous neuroretinal rim areas. J Glaucoma. 1995;4:314–6.
25. Jonas JB, Papastathopoulos K. Ophthalmoscopic measurement of the optic disc. Ophthalmology. 1995;102:1102–6.
26. Ruben S. Estimation of optic disc size using indirect biomicroscopy. Br J Ophthalmol. 1994;78:363–4.
27. Artes PH, Chauhan BC. Longitudinal changes in the visual field and optic disc in glaucoma. Prog Retin Eye Res. 2005;24:333–54.
28. Miglior S. Results of the European Glaucoma Prevention Study. Ophthalmology. 2005;112:366–75.
29. De Moraes CG, Liebmann JM, Park SC, Teng CC, Nemiroff J, Tello C, et al. Optic disc progression and rates of visual field change in treated glaucoma. Acta Ophthalmol. 2013;91(2):e86–91.
30. Healey PR, Mitchell P, Smith W, Wang JJ. Optic disc hemorrhages in a population with and without signs of glaucoma. Ophthalmology. 1998;105:216–23.
31. Bengtsson B. Optic disc haemorrhages preceding manifest glaucoma. Acta Ophthalmol. 1990;68:450–4.

32. Airaksinen PJ, Mustonen E, Alanko HI. Optic disc haemorrhages precede retinal nerve fibre layer defects in ocular hypertension. Acta Ophthalmol. 1981;59: 627–41.
33. Airaksinen PJ, Tuulonen A. Early glaucoma changes in patients with and without an optic disc haemorrhage. Acta Ophthalmol. 1984;62:197–202.
34. Soares AS, Artes PH, Andreou P, Leblanc RP, Chauhan BC, Nicolela MT. Factors associated with optic disc hemorrhages in glaucoma. Ophthalmology. 2004;111:1653–7.
35. Siegner SW, Netland PA. Optic disc hemorrhages and progression of glaucoma. Ophthalmology. 1996;103: 1014–24.
36. Tuulonen A, Takamoto T, Wu DC, Schwartz B. Optic disk cupping and pallor measurements of patients with a disk hemorrhage. Am J Ophthalmol. 1987;103:505–11.
37. De Moraes CGV, Prata TS, Liebmann CA, Tello C, Ritch R, Liebmann JM. Spatially consistent, localized visual field loss before and after disc hemorrhage. Invest Ophthalmol Vis Sci. 2009;50:4727–33.

Optic Nerve: Heidelberg Retinal Tomography

3

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Core Messages

- Ensure the highest quality Heidelberg Retinal Tomography (HRT) image possible.
- Ensure that the patient's age and ethnicity are correctly entered as this information will determine which normative database is used for analysis.
- Interpret printout findings in the context of optic disc size and morphology; extremes of disc size and tilted discs may lie beyond the normative database.
- When interpreting an HRT printout, focus on a single parameter, such as the Moorfields Regression Analysis or Glaucoma Probability Score, because examination of many parameters simultaneously may lead to chance positive findings that are spurious.
- Two progression algorithms are native to the HRT-3 software, topographical change analysis, and trend analysis.
- Of the stereometric parameters, rim area has been shown to be repeatable, reliable, and is also clinically meaningful. It is therefore a good candidate for monitoring structural change over time.
- It is important to remember that HRT alone will never give sufficient information for the clinician to make management decisions. The HRT findings need to be interpreted in the context of the patient's risk factors and other aspects of the examination.

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3.1 What Indices Should I Use to Help Me Interpret the Heidelberg Retinal Tomograph Printout?

Before looking at a Heidelberg Retinal Tomograph (HRT) printout, it is important to understand why the test was ordered. The HRT has two roles in practice, first to assist the clinician in diagnosing glaucoma and second to assist the clinician in identifying glaucomatous progression.

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Table 3.1 HRT printouts available

Summarize single scan data
Minimal report
Moorfields report
OU quickview report
OU report (most commonly used)
Stereometric report
Stereometric with Moorfields report
Summarize progression
Trend report
Topographical change analysis (TCA) overview

The current HRT-3 software can generate eight different printouts (Table 3.1), two of which ("trend report" and "TCA overview") summarize progression algorithms; these will be discussed in question 3.3. The remaining six printouts ("minimal report," "Moorfields report," "OU Quickview Report," "OU Report," "Stereometric Report," and "Stereometric with Moorfields Report") summarize data from a single scan (in the case of OU reports—from both eyes) and should be used to help the clinician decide whether or not features of the optic nerve head (ONH) are suggestive of glaucomatous optic neuropathy. Information from HRT printouts alone will not be sufficient to make a diagnosis of glaucoma; this requires interpretation of the results in the context of patient history, clinical examination, and perimetry findings.

When faced with any HRT printout, the usual demographic features need to be checked—patient name, identification number, date of birth, and ethnicity. After confirming if one has the correct patient and ethnic database selected, the image quality should be assessed next to judge whether the scan is of sufficient quality for software analysis to be useful or credible. One method to assess image quality is to look for the mean pixel height standard deviation (MPHSD). A standard deviation of less than 40 μm is acceptable, but imaging technicians should aim for values lower than 20 μm. The MPHSD is not featured on the minimal report or Moorfields report. In the "Stereometric report" and the "Stereometric with Moorfields report" (Fig. 3.1), "Topography Std Dev" is found at the bottom of the "Stereometric Analysis ONH" table in the lower left hand corner. In the "OU quickview report" (Fig. 3.2), "Std Dev" is highlighted in bold above the images. The OU report provides a quality classification based on standard deviation, which varies from excellent to very poor (in Fig. 3.2 quality is very good for right eye and good for left eye). Good quality images are those with a standard deviation less than 30 μm.

In order to fully assess image quality, one should also personally inspect the topography image featured on the printout as it is possible for an image with low standard deviation to be grainy, "honeycombed," or have motion artifact which may make it unusable. Under these circumstances, the scan acquisition should be repeated; if image quality cannot be improved, the scan should either be discarded or interpreted with caution. When satisfied that an image is of sufficient quality, placement of the contour line at the ONH margin (inner margin of Elschnig's ring) should be checked and redrawn if not correct.

When assessing the HRT printout to identify whether the ONH falls outside the normal range of appearances, it is important to focus on only a few quantitative parameters because the HRT provides a great deal of data. If many parameters are assessed the probability of finding an abnormal *P* value by chance (and, therefore, a spurious result) is increased. Of the individual stereometric parameters, *rim area*, and *cup shape measure* are the most useful parameters which aid in the discrimination between normal and glaucomatous eyes [1]. These two are featured in the "OU

Fig. 3.1 (continued) normal limits" as the measured rim area (demarcated as the interface of *red* and *green* within the histogram) falls above the lower 95 % prediction interval. The inferotemporal sector is classified as borderline as the measured rim area falls below the lower 95 % prediction interval, but above the 99.9 % prediction interval. The overall Moorfields regression classification is given by the "worst" disc sector and is shown below the histograms, in this case "borderline." Between the histograms and the disc image with Moorfields regression analysis is a graph of the height of the disc margin contour (*green line*) above the reference plane (*red line*). This is reported as "nerve fiber layer thickness" in the HRT software. A battery of global stereometric parameter values is tabulated in the *bottom left hand corner* of the printout, along with their normal ranges. Values outside normal range are highlighted in *bold*

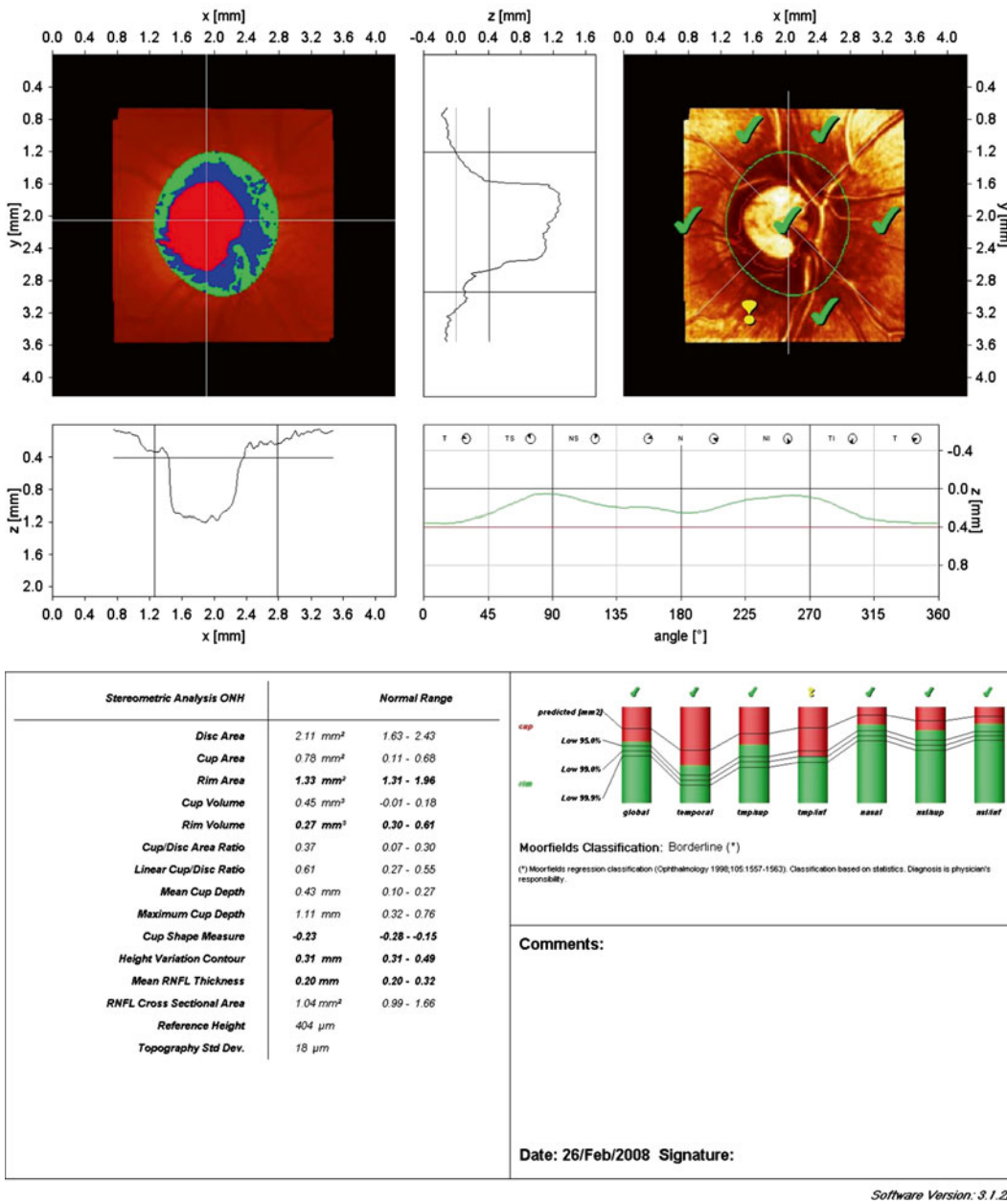

Fig. 3.1 Stereometric report with Moorfields regression analysis printout. The Moorfields regression analysis is summarized graphically in the *top right disc* image. In this particular disc, the inferotemporal disc sector is borderline (*yellow exclamation mark*) whereas the other disc sectors are within normal limits (*green ticks*), including the global classification (*central green tick*). The Moorfields regression analysis classification is explained with reference to the group of seven histograms shown in the *bottom right hand corner* of the printout. The histograms are split into two colors, *red* to represent "cup" area and *green* to represent "rim" area. Four lines are drawn through each histogram: from *top* to *bottom*, these lines represent the predicted rim area for a disc of that size, the lower 95 % prediction interval, the lower 99 % prediction interval, and the lower 99.9 % prediction interval. The majority of sectors are classified as "within

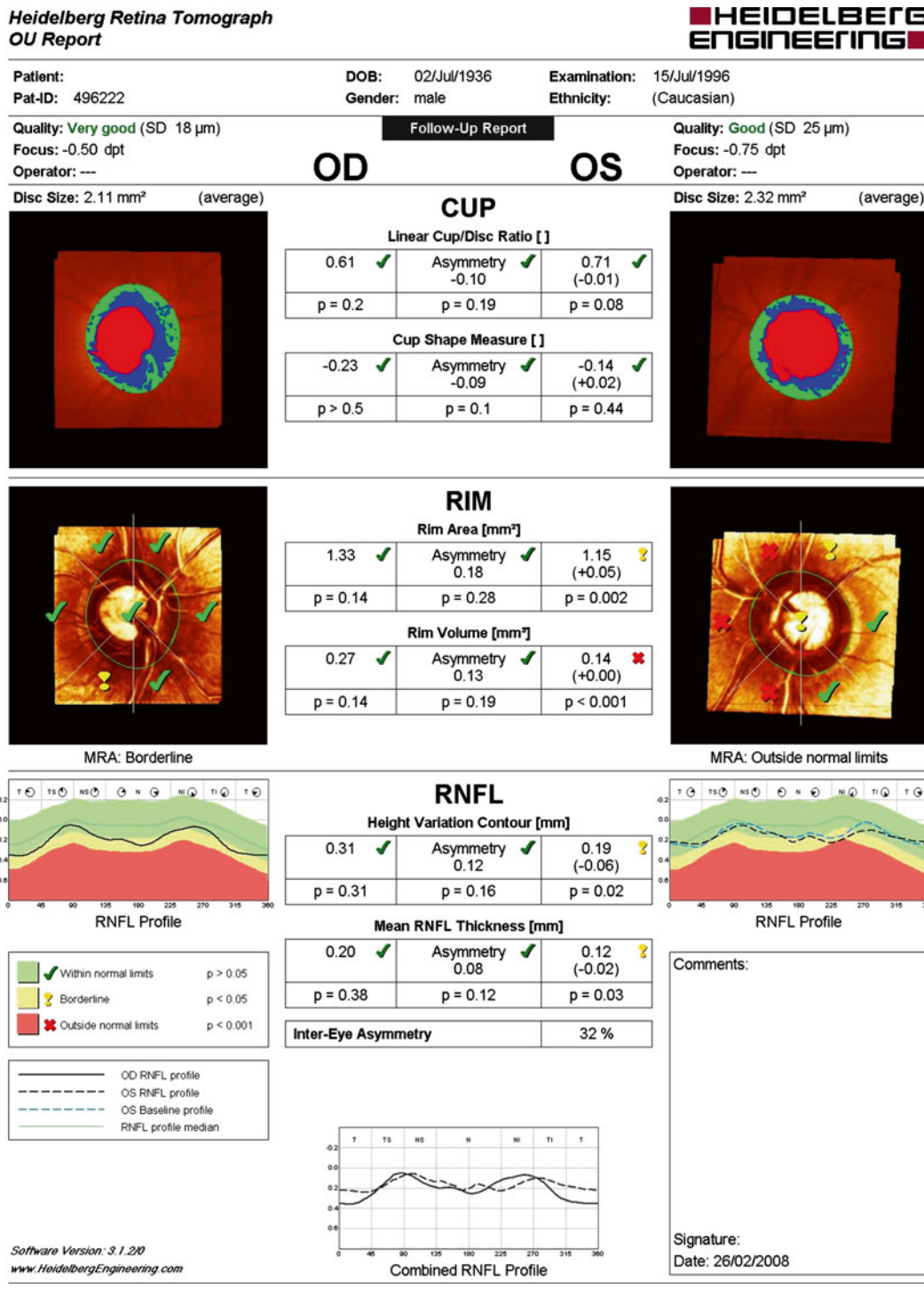

Fig. 3.2 OU report printout. Starting from the *top* of the printout, note that the image quality is classified for both eyes, based on the MPHSD, with very good image quality for the right eye and good image quality for the left eye. Below this, disc area is shown, as is its classification compared to a normative database—in this case average for both eyes. The OU report is then divided into three categories—"cup," "rim," and "RNFL." In the "cup category," linear cup-to-disc ratio is shown as well as cup shape measure. These values are not significantly outside of the normative range, and there is no significant inter-eye asymmetry. The *p*-values for these comparisons are shown, color coded with *green ticks* to indicate that the measurements are "within normal limits." In the "rim category," the graphical representations of the Moorfields regression analysis for both eyes are shown (Refer to Fig. 3.1 for

Report" in the middle column between images of the nerve heads (Fig. 3.2), which also highlight whether or not values are significantly outside the normal range. The retinal nerve fiber layer (RNFL) values included on the "OU Report" (mean RNFL thickness) are less useful because the RNFL is not measured directly by the HRT (HRT RNFL thickness is the height of ONH margin above the reference plane).

Of all the quantitative assessments available on the HRT printouts, the Moorfields regression analysis (MRA) (Fig. 3.1) is perhaps the most useful and user-friendly, given the clarity of the graphical display seen in the lower right corner. The "OU Report" (Fig. 3.2) also features MRA information directly on the reflectance images of the nerves (checks, crosses, and exclamation points on each sector) and highlights the overall classification in the center of the nerve (which is based on the most abnormal ONH sector).

One should remember that very large and very small ONHs can "confuse" the MRA [2, 3]. Results from such ONHs should, therefore, be interpreted with caution. ONH area ("disc area") can be found in the stereometric reports. It is also highlighted in the "OU Report" (Fig. 3.2), in which a classification of disc size with respect to the normative range is given above the topographical nerve image (average, above average, and below average). One should also look out for "atypical" ONH morphology, such as marked tilting, as these nerves often fall outside the MRA normative data range but are not necessarily glaucomatous.

A new classification system, the Glaucoma Probability Score (GPS; Fig. 3.3), has similar classification performance to the MRA with the advantage that an optic disc contour line is not required. Classification as abnormal is more likely with larger ONH sizes on both MRA and GPS, although the effect is more pronounced with the GPS [2]. The GPS is not featured on any of the HRT printouts and so needs to be viewed at the machine terminal.

Summary for the Clinician

- HRT can assist in diagnosing glaucoma and glaucoma progression in the context of other information the clinician has about the patient. It cannot diagnose glaucoma by itself.
- HRT 3 can produce eight different printouts (see Table 3.1).
- When interpreting HRT images, first confirm that demographic data is correctly entered as this affects the normative database used.
- Second, image quality should be assessed. MPHSD ideally should be less than 20 μm and is listed as "standard dev" or "SD" on many of the printouts.
- Standard deviation alone does not ensure good image quality and so the image should be examined for artifacts.
- Third, a contour line around the ONH margin should be correctly placed.
- The most useful parameters in discriminating normal and glaucomatous eyes are rim area and cup shape measure.
- RNFL thickness is less useful on HRT because it is not directly measured by the instrument.

Fig. 3.2 (continued) detailed explanation). In this subject, the overall Moorfields regression classification of the right eye is "borderline" whereas for the left eye it is "outside normal limits." Comparisons of rim area and rim area volume values against the normative database and between eyes are also shown. The *left* global rim area value is "borderline," as represented by a *yellow exclamation mark* and the *left* rim volume is outside normal limits, represented by a *red cross*. The "RNFL category" illustrates similar comparisons for height variation contour and mean RNFL thickness; the values for both of these parameters are "borderline" in the left eye of this subject. RNFL profile maps for each eye are also shown, along with a combined right and left eye RNFL profile, at the *bottom* of the printout. Although these profile maps are similar to what may be seen in OCT-based software algorithms, it should be noted that unlike in the OCT, RNFL thickness is measured indirectly using the HRT. The RNFL profile maps should therefore be interpreted with caution

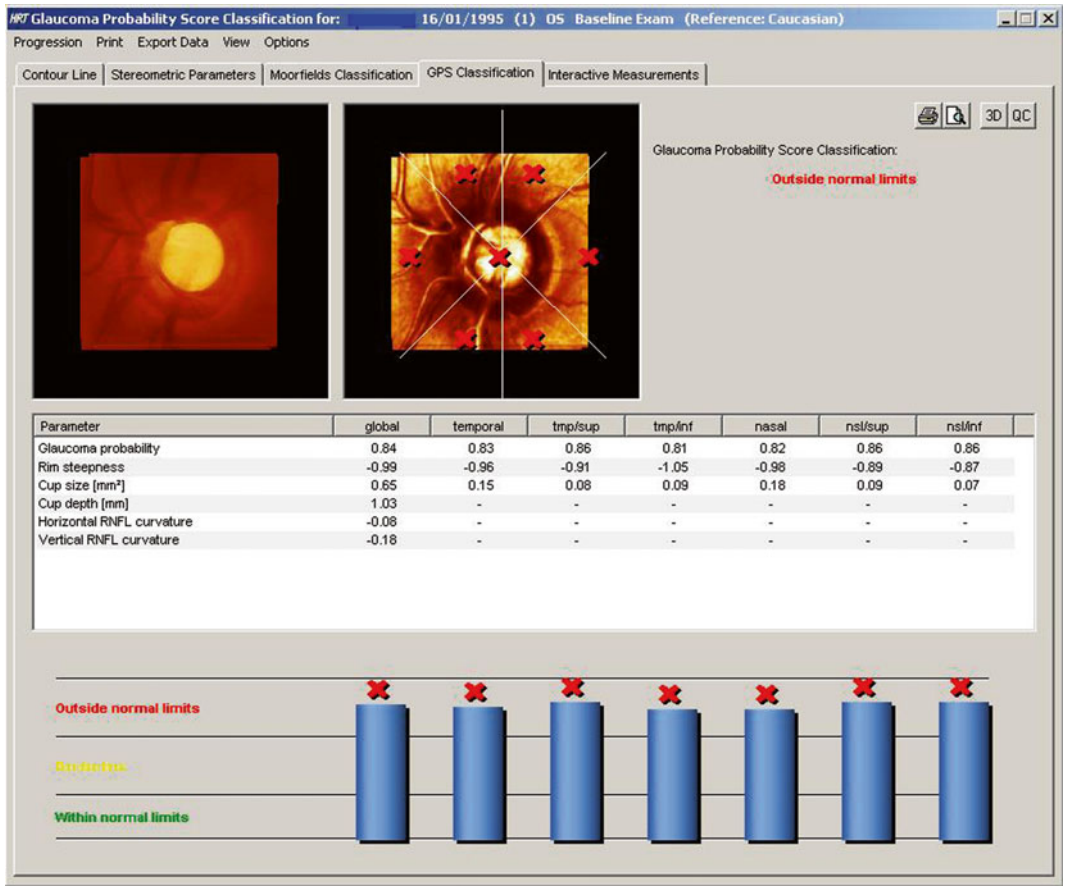

Fig. 3.3 Screen capture of Glaucoma Probability Score. This analysis is not available as an HRT printout. The *right hand disc* image demonstrates that all six HRT sectors, as well as the global classification, are outside normal limits (*red crosses*). This classification is reiterated in the series of histograms shown in the *bottom* half of the screen capture. The overall GPS classification is outside normal limits. The GPS scores, as well as the parameters from which the score is derived, are shown in the *middle* table

- The MRA is the most user-friendly quantitative assessment to examine.
- ONHs that are extremely small or large or atypical can lead to spurious MRA results.
- The GPS, which must be viewed on the computer screen, is similar to MRA but does not require drawing a contour line.

3.2 How Big a Change Is Meaningful in the Numbers on an HRT Printout?

Test–retest studies have identified rim area as the most repeatable and reliable stereometric parameter [4]. It is also a clinically meaningful parameter that is familiar to glaucoma clinicians, and

Table 3.2 Showing between-observer, between-visit repeatability coefficients for global rim area (using the 320 μm reference plane) at three levels of image quality

Image quality	Global rim area repeatability coefficient (mm^2)
Good (SD < 21)	0.07
Medium (SD 21–35)	0.09
Poor (SD > 35)	0.27

therefore, is a good candidate for identifying change over time. For the reasons given in Sect. 3.1, when assessing change it is advisable to focus on one stereometric parameter. When evaluating many parameters simultaneously it is more likely that false positive changes will be identified. The MRA and GPS classification algorithms are not useful for identifying change. These algorithms only have three classification levels—within normal limits, borderline, and outside normal limits—and a great deal of change may occur before a nerve sector crosses into the next classification level. In addition, measurement variability can cause "flip-flopping" between classification levels.

Rim area variability is highly dependent on the reference plane's position [4]. The reference plane lies parallel to the retinal surface; all structures above the plane (and within the ONH margin contour) are denoted as rim and those structures below as cup. The default reference plane in the HRT-3 software is the Standard Reference Plane, which is located 50 μm posterior to the temporal ONH margin. There is evidence that alternative reference planes, such as the 320 μm reference plane, generate less variable rim area measurements [5–7]. Strouthidis et al. have published repeatability coefficients for rim area using the HRT and HRT-II [5]. The repeatability coefficient is the British Standards Institution gauge of measurement error; 95 % of repeated measurements can be expected to fall within this margin of error [8]. In this study, repeatability varied with image quality. The coefficients for global rim area at three different levels of image quality (based on MPHSD) are shown in Table 3.2. When the Standard Reference Plane is applied to calculate the repeatability coefficients a slightly greater change is needed to denote significant change. Using the data in Table 3.2, with good image quality, 95 % of repeated global rim area measurements will be within a measurement error of 0.07 mm^2. Therefore, a decrease in global rim area of 0.071 mm^2 or more would be considered suspicious of glaucomatous change and not likely due to measurement error. If subsequent HRT tests continue to show a decrease in global rim area greater than this number, this would confirm that the rim is becoming thinner.

Because of measurement variability, it is advisable to look for sustained change over many tests. This principle underpinned a progression algorithm recently published that utilized sector rim area repeatability coefficients [9]. Unfortunately, the technique is not yet available on the HRT-3 software, and the published repeatability coefficients cannot be applied to the stereometric printout as this does not feature "sector" data (but only global data).

Summary for the Clinician

- Variability of measurements is highly dependent on the specific reference plane and on image quality.
- There are repeatability coefficients published for global rim area based on HRT and HRT-II images.
- There are repeatability coefficients published for sector rim area; however, they are not available for use with the currently available HRT-3 software.
- Sustained change over many tests is required to detect progression, given the possibility of significant measurement variability (test–retest variation).

3.3 How Does the HRT Detect Progression?

The HRT-3 software features two progression algorithms—trend analysis and topographical change analysis (TCA).

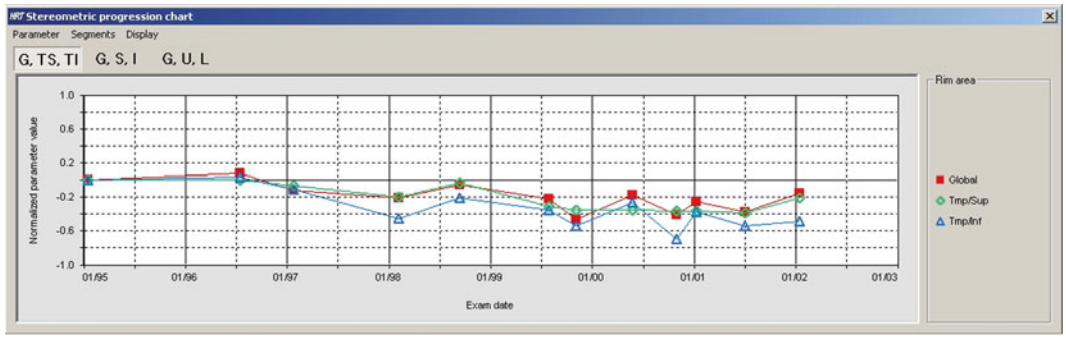

Fig. 3.4 Screen capture of the rim area trend analysis (parameter being followed is seen in the *top right corner*). It is not possible to print out individual parameter analyses. This trend analysis is from the left eye of a patient diagnosed with ocular hypertension at the time of the baseline measurement. Three trend graphs are shown; a *red line* for global rim area, a *green line* for superotemporal rim area, and a *blue line* for inferotemporal rim area. Each imaging date is demarcated by a *red square*, *green circle*, and a *blue triangle*, respectively. The trend demonstrates a generalized decrease in rim area over time, particularly in the inferotemporal sector. Note the variability of rim area measurements

3.3.1 Trend Analysis

The trend analysis generates graphs of the "normalized" change from baseline of a parameter over time. Normalization is achieved by using the ratio of the difference between an observed value and the baseline value to the difference between the mean value in a "normal" eye and one with advanced glaucoma ([observed parameter value minus baseline parameter value] divided by [mean parameter value in normal eye minus mean parameter value in advanced glaucoma eye]). The trend is therefore scaled from +1 (maximal improvement) to −1 (maximal deterioration). At the machine terminal, one can select "rim area trend" from the parameter drop down menu. Unfortunately, one cannot print this analysis (Fig. 3.4). The trend report generates graphs of average parameter values (Fig. 3.5). A major shortcoming of this technique is that interpretation is empirical, as it is not possible to quantify the rate of change.

3.3.2 Topographical Change Analysis

TCA monitors progression by measuring changes in surface (topographical) height within the HRT image [10]. This is done in groups of pixels (superpixels). The statistical method estimates the probability that chance alone is responsible for the difference in surface height at a superpixel between baseline and follow-up images, with progression being flagged when the change exceeds calculated measurement variability and is confirmed in subsequent images. TCA generates a "change probability map." This is the reflectance image overlaid with color-coded pixels. Green pixels have significant height elevation compared to baseline, whereas red pixels are significantly depressed. The color saturation indicates the depth of change (the more saturated, the greater the depth of change). In the current software, progression is defined as a cluster of 20 or more significantly depressed superpixels within the ONH margin. The software plots the area and volume of a significant cluster of superpixels over time (Fig. 3.6). The volume and area plots are at the top right of the printout. Rates of change are not calculated, but inspection of the plots allows an easy appreciation of trends of change over time.

The quality of the baseline image is particularly important to obtain a good TCA, so special attention should be given to image acquisition. The imaging technician should be instructed to acquire several images and to select the best quality image as the baseline. Before evaluating the TCA analysis, the image series should be checked

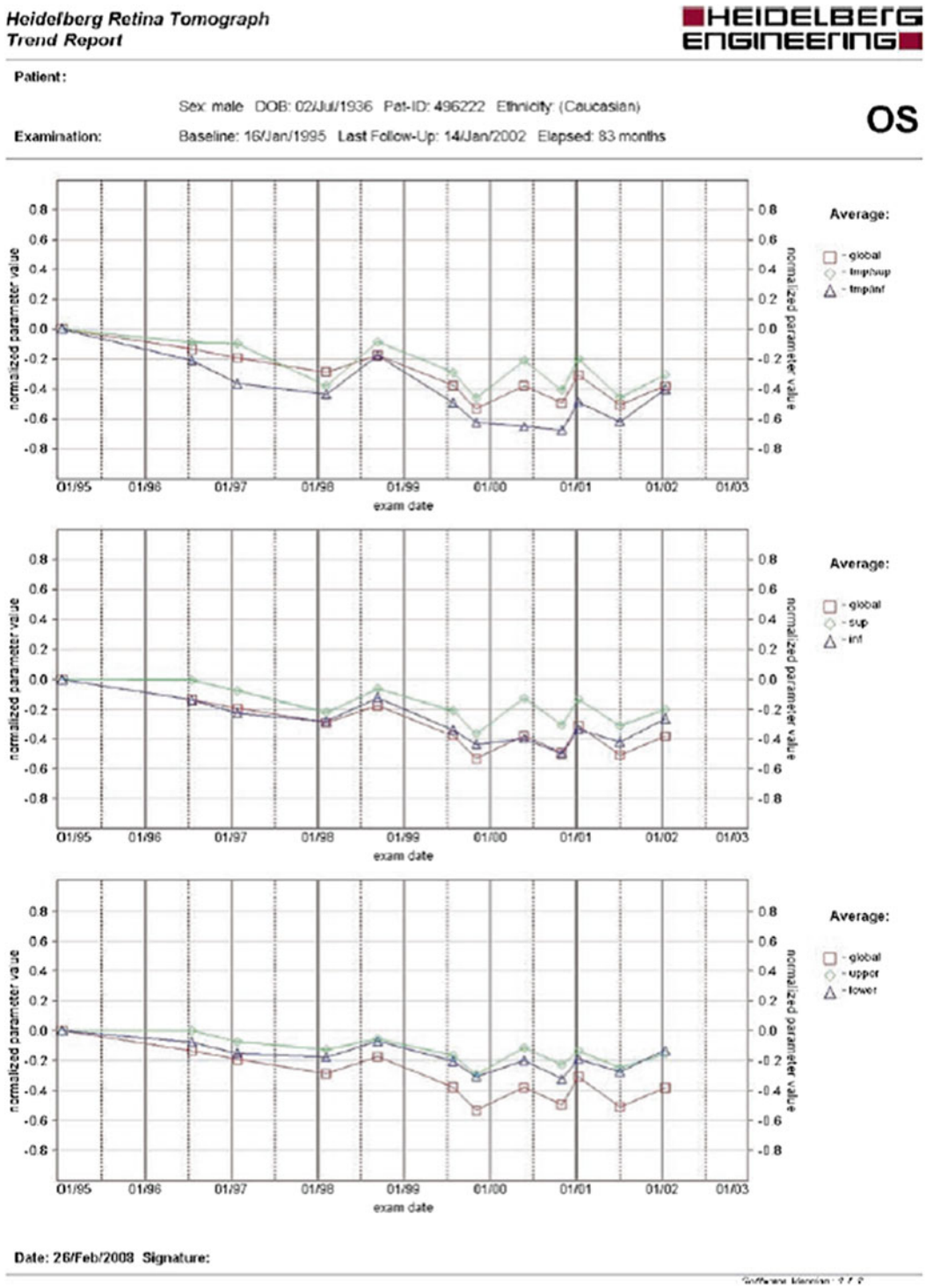

Fig. 3.5 Trend report printout for the same eye featured in Fig. 3.4. The graphs show change in average parameter values over time. The *upper* graph demonstrates global, superotemporal, and inferotemporal average parameter values over time. The *middle* graph demonstrates global, superior (combined superotemporal and superonasal sectors), and inferior (combined inferotemporal and inferonasal sectors) average parameter values over time. The *lower* graph demonstrates global, *upper* (superotemporal, superonasal, *upper half* of temporal and nasal sectors combined), and *lower* (inferotemporal, inferonasal, *lower half* of temporal and nasal sectors combined) average parameter values over time. The trend analyses shown demonstrate a decrease in average stereometric parameter values over time

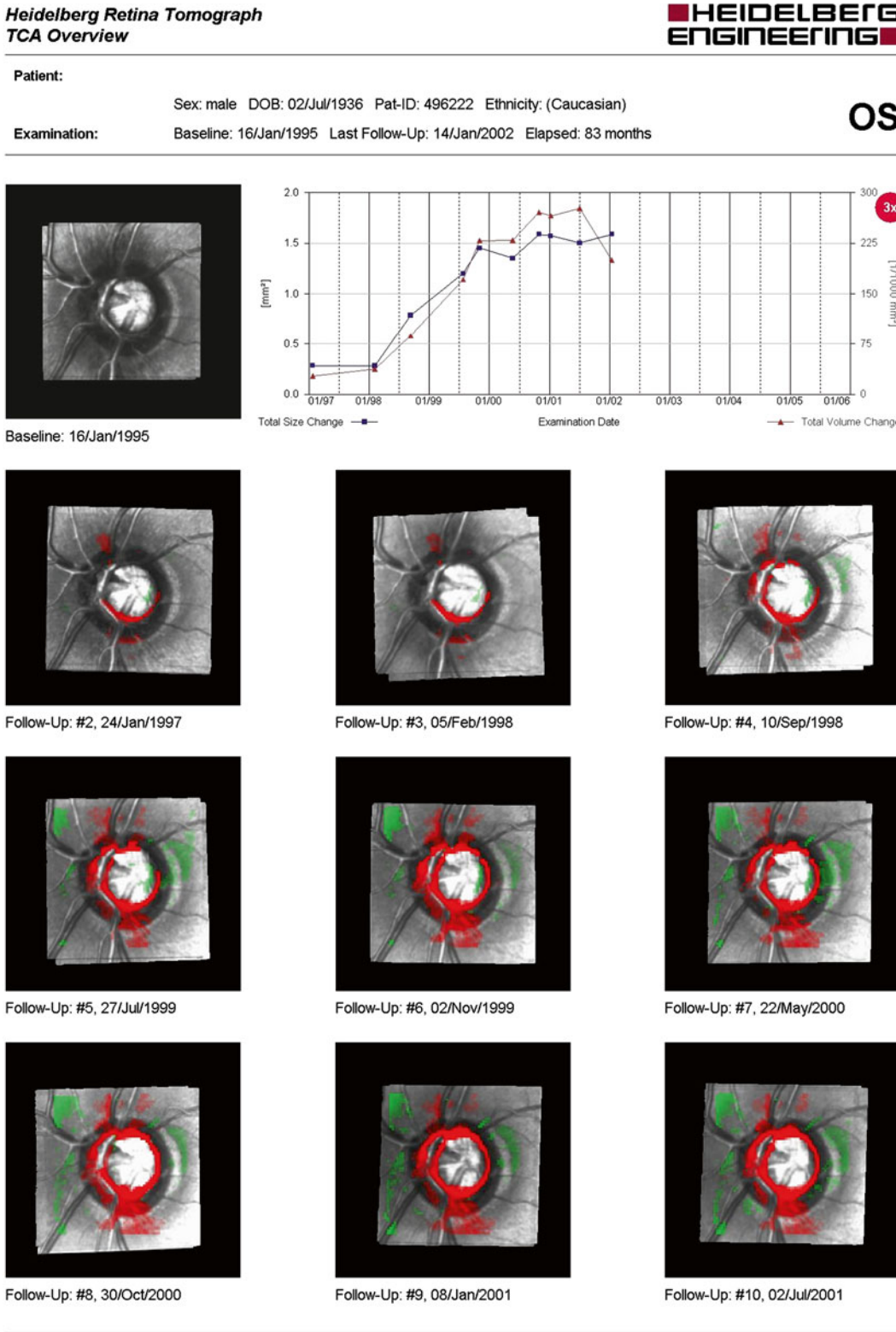

Fig. 3.6 TCA overview printout for the same eye as in Fig. 3.4. The appearance of *red* pixels in follow-up images represents significant surface height depression compared to baseline; *green* pixels represent significant surface height elevation. There is clear evidence of significant surface height depression, initially at the inferior pole of the

to ensure that all images are correctly aligned to the baseline. Misaligned images may be aligned manually or excluded from the series (if manual alignment is not possible). Similarly, poor quality images may be excluded.

A number of alternative progression strategies have been proposed, including linear regression of rim area over time [11], an event analysis based on rim area test–retest repeatability coefficients [9], and statistic image mapping [12]. Although these strategies have shown promise, none has yet been incorporated into the HRT software. It is possible, with basic statistical software, to replicate the first two techniques by outputting the HRT data into an excel spreadsheet. However, this is too laborious and time-consuming to be suitable for clinical practice.

Summary for the Clinician

- Trend analysis represents progression of a parameter over time through a graph of normalized change (−1 to +1) from baseline.
- TCA represents progression by statistically estimating the probability that change in height at a superpixel is by chance.
- TCA flags progression when change exceeds measurement variability and is confirmed on multiple tests; progression is defined as a cluster of 20 or more significantly depressed superpixels within the ONH margin.
- Image quality, particularly of the baseline image, is very important to progression algorithms.
- Newer progression algorithms have been proposed but none as yet has been incorporated into clinically available software.

3.4 Can I Use the HRT Clinically to Diagnose Glaucoma and Glaucomatous Progression? How Certain Can I Be that the Progression Is Real?

It is important to reiterate the fact that the HRT will never be able to replace sound clinical judgement. It is important to place the results of the HRT in the broader context of patient's risk factors, clinical examination, and functional testing. First, the clinician needs to assess the validity of the test—image quality, ONH margin contour placement, ONH type (tilted, large, myopic, etc.), and appropriateness of the normative data for the specific ONH type. Next, as suggested by Garway-Heath and Friedman, software analysis may be used to modify the "probability" of the patient having glaucoma [13]. To this end, the clinician should have some preconceived notion of whether or not the patient has glaucoma before ordering the test (a pretest probability), and then reassess this probability after the test (the posttest probability). In other words, has the HRT analysis made the diagnosis of glaucoma more likely or less likely? This concept is particularly useful in a busy clinic, where there are time and manpower constraints, because it allows the clinician the discretion to use the test only in patients in whom the results are likely to be helpful.

The likelihood ratio—the ratio of the probability that a particular test result would occur in a patient with the disease compared with the probability of the same result in a person without disease—is a particularly useful statistic in assessing the impact of a test. Zangwill and coworkers demonstrated that an abnormal overall MRA classification had a moderate to large effect on posttest probability of glaucoma (likelihood ratios range 5.99 to infinity), performing

Fig. 3.6 (continued) disc in the first two follow-up images, followed by superior polar change. Within 5 years, profound generalized surface height depression is evident. Graphs of the size and volume of a cluster of significantly depressed pixels over time are included in the *top right hand corner* of the printout. An increase in size and volume of the cluster over time is clearly shown

slightly better than an outside normal limits GPS classification [3]. Interestingly GPS had a lower likelihood ratio than MRA for a "within normal limits" classification (0.014–0.18 and 0.2–0.5, respectively). This suggests that an abnormal MRA classification may be useful in confirming that an ONH is suspicious, whereas a normal GPS classification is useful for confirming that an ONH is not suspicious.

Of the available progression algorithms, TCA is probably more useful in clinical practice than trend analysis, the shortcomings of which have been discussed above in Sect. 3.3. Deciding whether or not change identified on TCA is "real" is not straightforward because (1) there are little published data relating TCA parameters to long-term visual outcome measures and (2) because of differences between the software analysis and clinical approaches to change evaluation. In a clinical evaluation, a number of different features are assessed to decide whether or not the glaucomatous neuropathy is progressing—change in cup-to-disc ratio, presence of splinter hemorrhages, evolution of focal notching, changes in rim contour, and changes to blood vessels. TCA, on the other hand, only identifies change in topographical height—which may only indirectly be related to clinical corollaries; surface height change is difficult to identify by ophthalmoscopic examination. This discrepancy was highlighted in a study that compared glaucoma detection by expert observation of stereophotographs against TCA [14]. The study found agreement in only 65 % of cases; 6 % of nerves were found to progress by inspection of stereophotographs alone, whereas 30 % were identified as progressing by TCA alone. One cannot be certain whether or not the progression seen in that 30 % by TCA was genuine because of the lack of a "gold standard" method of defining glaucomatous progression. This means that one can never directly measure sensitivity (true positive) or specificity (true negative) of the HRT progression algorithms.

One way around the lack of a gold standard is to estimate specificity using proxy measures. Strouthidis et al. have estimated specificity using the proportion of normal subjects (without glaucoma risk factors) "progressing" and the proportion of subjects (both ocular hypertensive and normal) showing "improvement" in parameters [11]. The estimates work on the assumption that normal subjects should not demonstrate change in the direction of glaucoma and that any one parameter (in particular rim area) should not demonstrate significant improvement over time. In this way, it is possible to tailor a progression criterion to ensure a high specificity (high true negative rate; low false positive rate). Where estimated specificity is high, one can assume that any observed changes are likely to be genuine. As with the classification algorithms, the output of the progression analyses needs to be interpreted within a wider clinical context, keeping in mind the "pretest" probability that progression may be taking place.

Summary for the Clinician

- Glaucoma and glaucomatous progression can only be diagnosed in the context of the clinical picture (patient's risk factors, clinical exam, and functional testing results).
- A pretest and posttest probability of glaucoma or progression should be applied to make HRT results additive to clinical impressions.
- Agreement regarding glaucomatous progression between glaucoma experts examining optic nerve stereophotographs and TCA was only 65 %.
- There is no gold standard method of defining glaucomatous progression against which to measure TCA and clinician evaluation, however, specificity can be estimated using proxy measures.

References

1. Ferreras A, Pablo LE, Larrosa JM, et al. Discriminating between normal and glaucoma-damaged eyes with the Heidelberg retina tomograph 3. Ophthalmology. 2008;115:775–81.
2. Coops A, Henson DB, Kwartz AJ, Artes PH. Automated analysis of Heidelberg retina tomograph optic disc images by glaucoma probability score. Invest Ophthalmol Vis Sci. 2006;47(12):5348–55.
3. Zangwill LM, Jain S, Racette L, et al. The effect of disc size and severity of disease on the diagnostic accuracy of the Heidelberg Retina Tomograph Glaucoma Probability Score. Invest Ophthalmol Vis Sci. 2007;48(6):2653–60.
4. Strouthidis NG, White ET, Owen VM, et al. Factors affecting the test-retest variability of Heidelberg retina tomograph and Heidelberg retina tomograph II measurements. Br J Ophthalmol. 2005;89(11): 1427–32.
5. Strouthidis NG, White ET, Owen VM, et al. Improving the repeatability of Heidelberg retina tomograph and Heidelberg retina tomograph II rim area measurements. Br J Ophthalmol. 2005;89(11):1433–7.
6. Tan JC, Garway-Heath DF, Hitchings RA. Variability across the optic nerve head in scanning laser tomography. Br J Ophthalmol. 2003;87(5):557–9.
7. Tan JC, White E, Poinoosawmy D, Hitchings RA. Validity of rim area measurements by different reference planes. J Glaucoma. 2004;13(3):245–50.
8. British Standards Institution. Precision of test methods I: Guide for the determination and reproducibility for a standard test method, Vol. BS 5497, Part 1. London: BSI; 1979.
9. Fayers T, Strouthidis NG, Garway-Heath DF. Monitoring glaucomatous progression using a novel Heidelberg retina tomograph event analysis. Ophthalmology. 2007;114(11):1973–80.
10. Chauhan BC, Blanchard JW, Hamilton DC, LeBlanc RP. Technique for detecting serial topographic changes in the optic disc and peripapillary retina using scanning laser tomography. Invest Ophthalmol Vis Sci. 2000;41(3):775–82.
11. Strouthidis NG, Scott A, Peter NM, Garway-Heath DF. Optic disc and visual field progression in ocular hypertensive subjects: detection rates, specificity, and agreement. Invest Ophthalmol Vis Sci. 2006;47(7): 2904–10.
12. Patterson AJ, Garway-Heath DF, Strouthidis NG, Crabb DP. A new statistical approach for quantifying change in series of retinal and optic nerve head topography images. Invest Ophthalmol Vis Sci. 2005;46(5):1659–67.
13. Garway-Heath DF, Friedman DS. How should results from clinical tests be integrated into the diagnostic process? Ophthalmology. 2006;113(9):1479–80.
14. Kourkoutas D, Buys YM, Flanagan JG, et al. Comparison of glaucoma progression evaluated with Heidelberg retina tomograph II versus optic nerve head stereophotographs. Can J Ophthalmol. 2007; 42(1):82–8.

Optic Nerve: Scanning Laser Polarimetry

4

Clinton W. Sheets and David S. Greenfield

Core Messages

- Scanning laser polarimetry (SLP) has undergone multiple hardware and software changes, particularly in neutralizing anterior segment birefringence, to improve its ability to recognize retinal nerve fiber layer retardation.
- Assessment of scan quality is critical before interpreting a report.
- The Nerve Fiber Indicator (NFI) is a statistical value that is useful in differentiating normal from glaucomatous eyes (typically with values of 50–100).
- The classifications of normal and abnormal in SLP are statistical; glaucoma diagnosis is a clinical decision.
- New software for evaluating glaucoma progression employs trend-based and event-based analyses, but has not been clinically validated yet.

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4.1 What Is the Physical Principle Behind Scanning Laser Polarimetry?

Scanning laser polarimetry (SLP) is a confocal scanning laser ophthalmoscope with an integrated polarimeter that measures the amount of retardation (phase shift) of a polarized, near-infrared laser beam as it passes through the retinal nerve fiber layer (RNFL) [6, 12, 18–22]. The RNFL is made of highly ordered parallel axon bundles. The axons contain microtubules, cylindrical intracellular organelles with diameters smaller than the wavelength of light. The highly ordered structure of the microtubules is the source of RNFL birefringence [20]. Different birefringence patterns are detected when the RNFL is healthy versus atrophied from glaucoma.

4.1.1 How Has Scanning Laser Polarimetry Evolved?

Since its introduction, SLP has undergone several hardware and software changes. The first generation device (Nerve fiber analyzer I or NFA I) became commercially available in 1992 and was equipped with a single detector, which was later replaced by a double detector (NFA II). Originally, it incorporated a fixed retarder to adjust for corneal birefringence because it was assumed originally that all individuals have the same slow axis

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of corneal birefringence. The total measured retardation was assumed to be solely the retardance of the RNFL.

The GDx Nerve fiber analyzer became commercially available in 1996. It included a normative database, consisting of 400 eyes and a blood vessel removal algorithm to augment reproducibility, matched for age and race. High reproducibility has been reported in phakic and pseudophakic eyes of normal and glaucomatous subjects [7, 27]. However, with previous iterations, the GDx Nerve fiber analyzer incorporated a fixed corneal compensator to neutralize corneal birefringence. Several studies have demonstrated that the magnitude and axis of corneal polarization are highly variable among individuals and that these variations strongly correlate with RNFL thickness assessments obtained with SLP [12, 21, 22, 34]. These individual differences produce erroneous RNFL thickness assessment in eyes that deviate from the fixed compensator settings.

4.1.2 What Is GDxVCC (Variable Corneal Compensation)?

GDxVCC (Carl Zeiss Meditec, Dublin, California, USA) was introduced in 2002 and is the current commercial iteration of this technology. GDxVCC provides individual customized compensation of anterior segment birefringence using retardation measurements obtained in the macula, based on the *form birefringence* shown by Henle's fiber layer (form birefringence is an optical property where light refracts differently in perpendicular planes due to the molecular organization of a material) [9, 17, 21, 22]. For eyes with macular pathology, a "screen method" [3] that uses multiple points over a large square area of the macula to neutralize corneal birefringence is commercially available. Several studies have shown that with GDxVCC, there is a significant improvement in the detection of the structure–function relationship [2–4, 15, 24–26, 28], agreement with other imaging technologies [2, 3, 8, 11], and discrimination of power for glaucoma detection [6, 13, 32, 35] as compared to prior generations of SLP, which utilized a fixed corneal compensation. A normative database consisting of approximately 540 eyes stratified by age and ethnicity is included. The image printout features a 20 by 20° reflectance map of the disc and peripapillary retina (Fig. 4.1). Retardation parameters are color coded to indicate statistical deviation from the normative database. Two-dimensional RNFL probability maps are available that indicate the statistical likelihood of glaucomatous damage.

4.1.3 What Is GDxECC (Enhanced Corneal Compensation)?

In a subset of eyes, GDxVCC scans show *atypical birefringence patterns* (Fig. 4.1) such that the brightest areas of the retardation maps are not consistent with the histologically thickest portions of the peripapillary RNFL located along the superior and inferior arcuate bundles. Enhanced corneal compensation (ECC) is a research platform that improves the signal-to-noise ratio and eliminates artifacts associated with atypical birefringence patterns [29–33]. The ECC algorithm introduces a predetermined birefringence bias to shift the measurement of the total retardation to a higher value region in order to remove noise and reduce atypical patterns. The amount of birefringence bias is determined using the birefringence pattern of the macular region, which is then mathematically removed point by point from the total birefringence pattern of the VCC to improve the signal and obtain a retardation pattern of the RNFL with the least noise [33].

Summary for the Clinician

- SLP measures the amount of retardation (phase shift) of polarized light as it passes through the RNFL and is a technology embodied in the commercially available GDxVCC.
- Compensation for corneal birefringence is critical in order to neutralize its confounding influence on RNFL thickness.

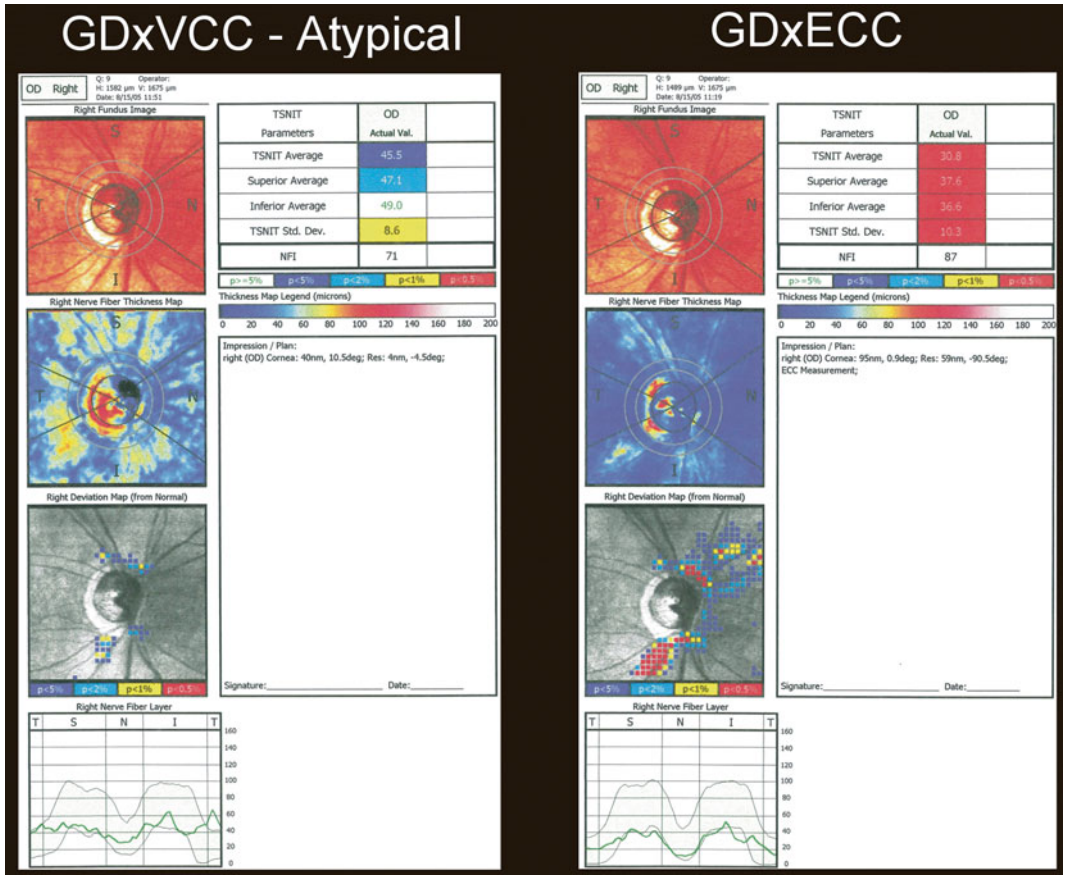

Fig. 4.1 Illustrates a right eye with glaucomatous optic neuropathy and significant atypical birefringence artifact on GDxVCC imaging (*left panel*). Note the alternating bands of high and low retardation throughout the parapapillary region limiting the identification of an RNFL abnormality on the deviation map. GDxECC imaging (*right panel*) demonstrates a marked reduction in artifact with superior and inferior RNFL atrophy noted on the deviation map and multiple abnormal retardation parameters

- Over the last decade, strategies to neutralize anterior segment birefringence have evolved considerably.
- GDxECC is a promising tool to further enhance signal and reduce noise associated with atypical birefringence artifact.
- Atypical birefringence patterns represent a common source of artifact and are characterized by alternating bands of high and low retardation in the nasal and temporal parapapillary regions. GDxECC eliminates this artifact.

4.2 How Is Image Quality and Artifact Assessed on the GDxVCC Printout?

A high-quality GDxVCC scan is sharply focused and well centered on the optic nerve with minimal eye movement and even illumination. GDxVCC uses a fixed scan circle of 3.2 mm diameter centered on the optic disc. Images with abnormal definition of the blood vessel borders or the optic nerve indicate eye movement and are unacceptable. The most recent software version automatically generates

a quality score—Q-score—between 1 and 10 and is based upon various factors, including fixation, refraction, and ocular alignment. A Q-score of 8 or greater is considered an acceptable quality score. It is important that corneal birefringence be adequately compensated for in order to accurately measure true RNFL birefringence. Eyes with residual corneal birefringence above 13 nm should be interpreted with caution (this value is found in the center of the printout under Impression/Plan).

Understanding the limitations of the various imaging technologies permits their appropriate use in the clinical setting. All imaging technologies, including optic disc photography, are affected by eye movement, ocular surface disease (such as moderate corneal epitheliopathy), cataract, and poor focus. Additionally, other factors may contribute to GDxVCC artifact [16]. Eyes with corneal pathology or prior corneal surgery, such as penetrating keratoplasty, may have uncompensated corneal birefringence that confounds RNFL assessment. Also, since strategies for corneal compensation involve measurements of macular retardation [21, 22], eyes with macular pathology may have disruption of Henle's fiber layer, which will lead to the failure of conventional methods to compensate for corneal birefringence. Alternative strategies for corneal compensation in eyes with macular pathology have been described [3]. Finally, a subset of myopic eyes, particularly those with RPE atrophy, generate considerable scleral reflectance and atypical patterns of birefringence characterized by a typical scan score (TSS) below 80 and radial spoke-like patterns of birefringence [1]. The TSS score is a reliability index ranging from 0 to 100 (lower scores are highly correlated with atypical patterns) that is currently only available via electronic data export, and at the time of writing, it is not found on the printout. Images with atypical birefringence patterns should be interpreted with caution.

Summary for the Clinician

- Clinicians should always review image quality prior to clinical interpretation of a printout.
- Unacceptable GDxVCC images have a Q-score less than 8, residual corneal birefringence greater than 13 μm, and abnormal definition of blood vessel edges or the optic nerve.
- Corneal pathology, corneal surgery, and macular pathology can lead to inadequate compensation of corneal birefringence and erroneous RNFL thickness assessment.
- Highly myopic eyes may not be easily imaged due to atypical patterns of birefringence.

4.3 Can I Use the Scanning Laser Polarimetry Report to Diagnose Glaucoma?

Glaucoma diagnosis is a clinical decision based upon clinical examination of the optic disc, parapapillary RNFL, and standard automated perimetry. However, GDxVCC provides statistical classifications that may facilitate glaucoma diagnosis. The GDxVCC report contains a number of images including a reflectivity (fundus) image, a retardation (RNFL thickness) image, a statistical deviation image, and the TSNIT graphs (RNFL profile plots) (Fig. 4.2).

The *reflectivity image* (*fundus*) at the top of the report displays the position of the peripapillary measurement annulus and allows an assessment of the annulus centration on the optic disc. Below the reflectivity image is the *retardation image* (*RNFL thickness*), which displays a "heat map" of RNFL thickness, with hotter colors representing

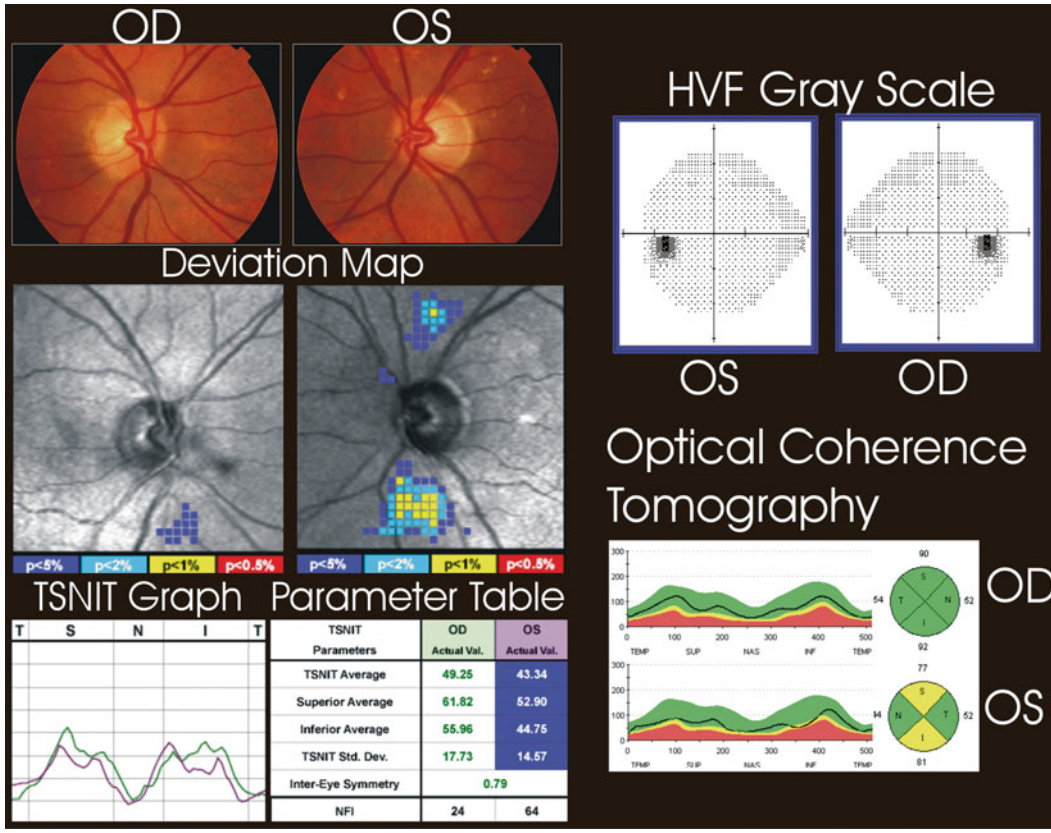

Fig. 4.2 Illustrates a patient with early exfoliation glaucoma in the left eye in whom GDxVCC imaging facilitated the diagnosis of glaucoma. Optic nerve photographs demonstrate asymmetric optic disc cupping in the left eye with diffuse neural rim atrophy. Note that the asymmetric cupping is not due to asymmetry in disc size. Standard automated perimetry was normal. GDxVCC imaging demonstrates diffuse RNFL atrophy (deviation map) along the superior and inferior arcuate bundles. Compared with age-matched normal controls, several GDxVCC retardation parameters are outside 95 % normal in the left eye including TSNIT Average, Superior Average and Inferior Average, TSNIT standard deviation, and NFI. Confirmatory testing using optical coherence tomography demonstrates RNFL atrophy in the superior and inferior parapapillary quadrants outside 95 % normal limits

greater retardation (and, therefore, thicker RNFL) values. In a normal RNFL thickness map, bright yellow and red (indicating thicker RNFL) are seen in the superior and inferior sectors, while green and blue (indicating thinner RNFL) are seen in the nasal and temporal sectors. Below this is the *statistical deviation map*, which highlights pixels with retardation values falling below those seen in the normative database (Fig. 4.2). The color of the pixel indicates the level of probability of deviation from normal, with the probability values (<1 %, <5 %, etc.) displayed in the upper central panel. This map allows the clinician to evaluate the anatomical distribution of abnormally low retardation. The *TSNIT graphs* (*RNFL profile plots*) at the bottom of the report display the RNFL thickness values around the measurement annulus in relation to the normal range of thickness values. The green and purple shaded areas indicate the normal range of values for the left and right eyes, respectively. In between these two graphs with shaded areas is the TSNIT symmetry graph with right and left eye plots superimposed on each other. Retardation parameters generated automatically by the software are displayed in the top central panel and include values for TSNIT average, superior average, inferior average, TSNIT standard deviation, inter-eye symmetry, and Nerve Fiber Index (NFI). These are color coded to indicate statistical deviation

from the normative database values. Inter-eye symmetry values near 1.0 represent good symmetry, and values near 0 represent poor symmetry.

A consensus regarding the definition of an abnormal scan has not been established. A GDxVCC scan may be considered abnormal if the TSNIT average, superior average, inferior average, TSNIT standard deviation, inter-eye symmetry or NFI is abnormal at the $p<1$ % level. A GDxVCC scan may be considered borderline if these same parameters fall outside normal at the $p<5$ % level. It has been suggested that the cutoff value for NFI is >50 at the $p<1$ % level and >30 at the $p<5$ % level [5]. Although there is no agreement regarding the ideal parameter for glaucoma diagnosis, studies have shown high levels of sensitivity and specificity using the NFI for glaucoma diagnosis. Finally, other mechanisms of nonglaucomatous RNFL atrophy must be considered when interpreting GDxVCC scans.

Summary for the Clinician

- Glaucoma is a clinical diagnosis and should not be established using any single parameter on GDxVCC or any single technology.
- Compared to a normative database stratified by age and ethnicity, GDxVCC facilitates glaucoma diagnosis by providing statistical classifications.
- Eyes with abnormalities in the GDxVCC statistical deviation map and/or TSNIT parameters outside 95 % normal limits may suggest RNFL atrophy and require clinical correlation.
  - There is no consensus regarding what defines an abnormal scan; however, a *p*-value <1 % for any measured/calculated parameter may be considered abnormal, while a *p*-value <5 % is considered borderline.
  - NFI has shown high levels of sensitivity and specificity for glaucoma diagnosis. NFI values greater than 50 are used as cutoff for the $p<1$ % level and greater than 30 is used for $p<5$ % level.

4.4 Can I Use Scanning Laser Polarimetry to Assess Progression of Optic Nerve Damage?

Established risk factors for the progression of ocular hypertension to glaucoma include increased age, intraocular pressure, cup-disc ratio, optic disc hemorrhage, and reduced central corneal thickness [10, 14, 23]. The confocal scanning laser ophthalmoscopy (CSLO) ancillary study to the Ocular Hypertension Treatment Study (OHTS) adds to this list by demonstrating that even when the optic disc is not classified by expert review of stereoscopic photographs as glaucomatous and the standard visual field is normal, certain optic disc features obtained using baseline Heidelberg retinal tomography (HRT) imaging are associated with development of primary open-angle glaucoma. In contrast, optic discs that were classified as being within normal limits at baseline with the HRT Moorfields regression analysis were unlikely to develop a glaucoma endpoint during the 5 years duration of analysis. This study provided the first evidenced-based validation for a glaucoma imaging technology. Similar studies demonstrating that certain structural changes can precede the observation of a glaucoma endpoint have also been performed with SLP. Mohammadi et al. [25] found that thinner baseline RNFL measurements using SLP in glaucoma suspects were independent predictors of subsequent visual field damage even when age, intraocular pressure, central corneal thickness, vertical cup-disc ratio, and visual field pattern standard deviation were included in a multivariate statistical model.

4.4.1 Detection of Progression with SLP

Recently, software has been introduced to the GDxVCC to assess serial images for the identification of progression (GDx Review with Guided Progression Analysis (GPA)™, Carl Zeiss Meditec, Dublin, CA, USA). The analysis software requires an external computer linked to the GDxVCC. In a manner similar to the Guided Progression Analysis with the Humphrey Field

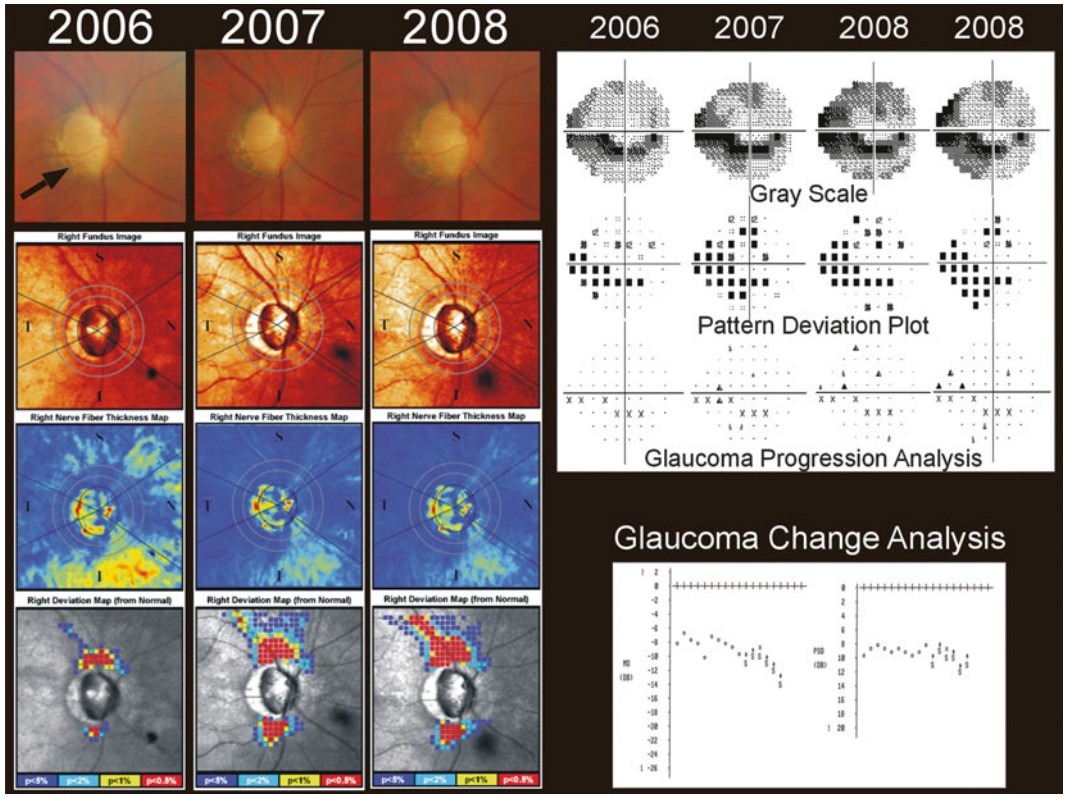

Fig. 4.3 Illustrates a right eye with progressive glaucomatous damage over a 2-year period of follow-up. Optic nerve photographs (*top left*) demonstrate an optic disc hemorrhage at the baseline examination with extensive atrophy of the inferior neural rim. Serial GDxVCC examinations show increased superior and RNFL atrophy on the deviation map (*bottom left*). GPA™ analysis (*top right*) using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA) shows a dense inferior arcuate scotoma and progressive enlargement of a superior nasal depression, and a trend analysis (*bottom right*) reveals a decline in the visual field mean deviation

Analyzer (Carl Zeiss Meditec, Dublin, CA, USA), confirmation of suspected RNFL progression (Fig. 4.3) requires detection of change on three consecutive follow-up images compared to an average of two high-quality baseline scans (Fig. 4.4). Prospective studies are still necessary to validate this progression strategy.

Three algorithms are used to evaluate statistically significant progression and changes are color coded: red demonstrates likely reduction in RNFL thickness, yellow indicates possible reduction, and purple indicates possible increase in RNFL thickness. Narrow focal RNFL change may be detected using the image progression map. A minimum 150 of 9000 contiguous pixels must show repeatable change using this strategy. Broader focal changes may be detected using the TSNIT progression graph, which identifies change when a minimum 4 of 64 adjacent segments around the calculation ellipse show change. Lastly, diffuse changes may be detected by the assessment of trends in three summary parameters (TSNIT average, superior average, and inferior average).

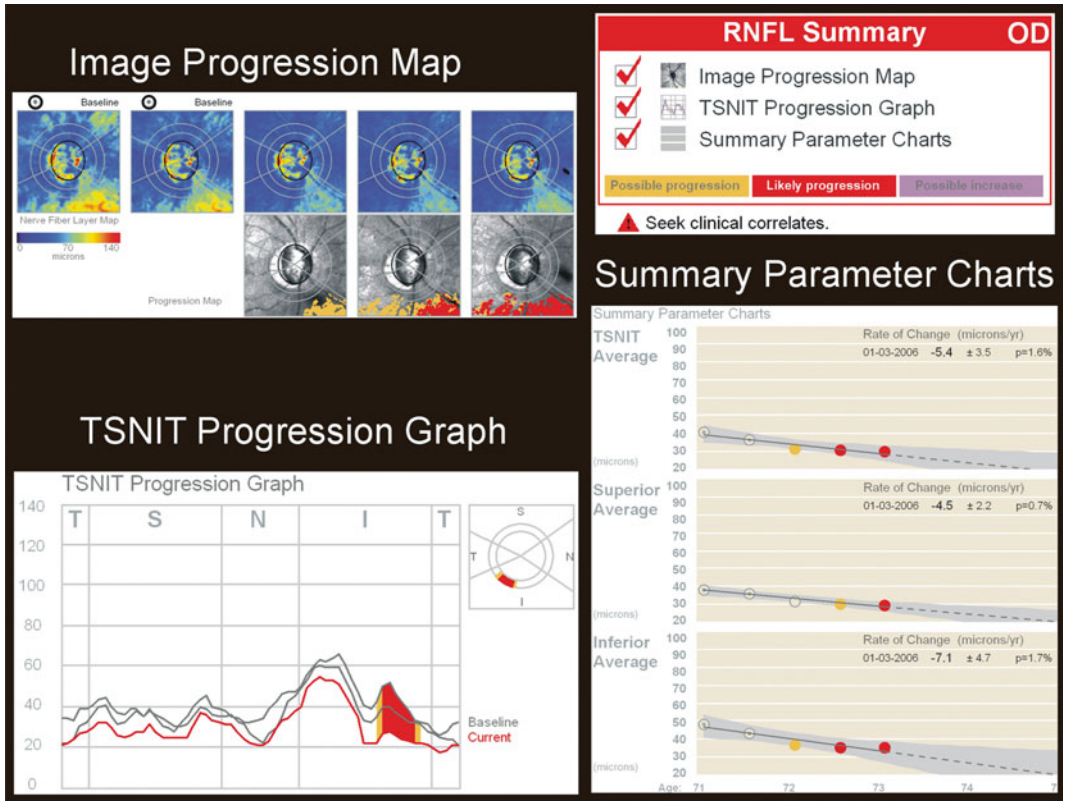

Fig. 4.4 Demonstrates serial assessment of GDxVCC images of the patient described in Fig. 4.3 by using GDx Review with Guided Progression Analysis™ (Carl Zeiss Meditec, Dublin, CA, USA). Likely progression of all three algorithms is identified in the RNFL summary box (*top right*). Progressive atrophy of the inferior RNFLT is visualized on both the image progression map (*top left*) and TSNIT progression map (*bottom left*). Significant reductions in the TSNIT average, superior average, and inferior average RNFL thickness parameters are illustrated in the summary parameter charts (*bottom right*)

Summary for the Clinician

- The ability of imaging technology to detect structural change before a traditional glaucoma endpoint is reached has been validated in a few studies; therefore, glaucoma suspects with RNFL atrophy detected using GDxVCC imaging may be at increased risk for subsequent progression to glaucoma.
- Progression analysis software for GDxVCC is under development and provides a means for differentiating test–retest variability from biological changes.
- There is insufficient evidence to validate the progression analysis software strategy at the present time; longitudinal studies are necessary to validate the sensitivity and specificity of this algorithm.
- Both structural and functional tests should be considered when making clinical decisions regarding progression.
- Clinical correlation should be performed, and treatment recommendations should be individualized.

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References

1. Bagga H, Greenfield DS, et al. Quantitative assessment of atypical birefringence images using scanning laser polarimetry with variable corneal compensation. Am J Ophthalmol. 2005;139:437–46.
2. Bagga H, Greenfield DS, et al. Scanning laser polarimetry with variable corneal compensation and optical coherence tomography in normal and glaucomatous eyes. Am J Ophthalmol. 2003;135:521–9.
3. Bagga H, Greenfield DS, et al. Scanning laser polarimetry with variable corneal compensation: Identification and correction for corneal birefringence in eyes with macular pathology. Invest Ophthalmol Vis Sci. 2003;44:1969–76.
4. Bowd C, Zangwill LM, et al. Association between scanning laser polarimetry measurements using variable corneal polarization compensation and visual field sensitivity in glaucomatous eyes. Arch Ophthalmol. 2003;121:961–6.
5. Carl Zeiss. GDx primer Chapter 4. http://www.zeiss.de/C125679E00525939/EmbedTitelIntern/GDxprimerChapter4/$File/GDx_Primer_Chapter4.pdf. Accessed 24 Aug 2007.
6. Choplin NT, Zhou Q, et al. Effect of individualized compensation for anterior segment birefringence on retinal nerve fiber layer assessments as determined by scanning laser polarimetry. Ophthalmology. 2003;110:719–25.
7. Colen TP, Tjon-Fo-Sang MJH, et al. Reproducibility of measurements with the nerve fiber analyzer (NFA/GDx). J Glaucoma. 2000;9:363–70.
8. Essock EA, Sinai MJ, et al. Fourier analysis of optical coherence tomography and scanning laser polarimetry retinal nerve fiber layer measurements in the diagnosis of glaucoma. Arch Ophthalmol. 2003;121:1238–45.
9. Garway-Heath DF, Greaney MJ, et al. Correction for the erroneous compensation of anterior segment birefringence with the scanning laser polarimeter for glaucoma diagnosis. Invest Ophthalmol Vis Sci. 2002;43:1465–74.
10. Gordon MO, Beiser JA, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:714–20.
11. Greenfield DS, Bagga H, et al. Macular thickness changes in glaucomatous optic neuropathy detected using optical coherence tomography. Arch Ophthalmol. 2003;121:41–6.
12. Greenfield DS, Huang X-R, et al. Effect of corneal polarization axis on assessment of retinal nerve fiber layer thickness by scanning laser polarimetry. Am J Ophthalmol. 2000;129:715–22.
13. Greenfield DS, Knighton RW, et al. Correction for corneal polarization axis improves the discriminating power of scanning laser polarimetry. Am J Ophthalmol. 2002;134:27–33.
14. European Glaucoma Prevention Study Group, Miglior S, et al. Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. Ophthalmology. 2007;114:3–9.
15. Hoffmann EM, Medeiros FA, et al. Relationship between patterns of visual field loss and retinal nerve fiber layer thickness measurements. Am J Ophthalmol. 2006;141(3):463–71.
16. Hoh ST, Greenfield DS, et al. Factors affecting image acquisition during scanning laser polarimetry. Ophthalmic Surg Lasers. 1998;29:545–51.
17. Huang XR, Knighton RW. Linear birefringence of the retinal nerve fiber layer measured in vitro with a multispectral imaging micropolarimer. J Biomed Opt. 2002;7:199–204.
18. Huang XR, Knighton RW. Diattenuation and polarization preservation of retinal nerve fiber layer reflectance. Appl Opt. 2003;42(28):5737–43.
19. Huang XR, Knighton RW. Theoretical model of the polarization properties of the retinal nerve fiber layer in reflection. Appl Opt. 2003;42(28):5726–36.
20. Huang XR, Knighton RW. Microtubules contribute to the birefringence of the retinal nerve fiber layer. Invest Ophthalmol Vis Sci. 2005;46(12):4588–93.
21. Knighton RW, Huang X-R. Analytical methods for scanning laser polarimetry. Opt Express. 2002;10:1179–89.
22. Knighton RW, Huang X-R, et al. Analytical model of scanning laser polarimetry for retinal nerve fiber layer assessment. Invest Ophthalmol Vis Sci. 2002;43:383–92.
23. Medeiros FA, Weinreb RN, et al. Validation of a predictive model to estimate the risk of conversion from ocular hypertension to glaucoma. Arch Ophthalmol. 2005;123(10):1351–60.
24. Medeiros FA, Zangwill LM, et al. Influence of disease severity and optic disc size on the diagnostic performance of imaging instruments in glaucoma. Invest Ophthalmol Vis Sci. 2006;47(3):1008–15.
25. Mohammadi K, Bowd C, et al. Retinal nerve fiber layer thickness measurements with scanning laser polarimetry predict glaucomatous visual field loss. Am J Ophthalmol. 2004;138:592–601.
26. Reus NJ, Lemij HG. Scanning laser polarimetry of the retinal nerve fiber layer in perimetrically unaffected eyes of glaucoma patients. Ophthalmology. 2004;111(12):2199–203.
27. Rhee DJ, Greenfield DS, et al. Reproducibility of retinal nerve fiber layer thickness measurements using scanning laser polarimetry in pseudophakic eyes. Ophthalmic Surg Lasers. 2002;33:117–22.

28. Schlottman PG, De Cilla S, et al. Relationship between visual field sensitivity and retinal nerve fiber layer thickness as measured by scanning laser polarimetry. Invest Ophthalmol Vis Sci. 2004;45:1823–9.
29. Sehi M, Guaqueta DC, et al. Scanning laser polarimetry with variable and enhanced corneal compensation in normal and glaucomatous eyes. Am J Ophthalmol. 2007;143:272–9.
30. Sehi M, Guaqueta DC, et al. An enhancement module to improve the atypical birefringence pattern using scanning laser polarimetry with variable corneal compensation. Br J Ophthalmol. 2006;90:749–53.
31. Sehi M, Ume S, et al. Scanning laser polarimetry with enhanced corneal compensation and optical coherence tomography in normal and glaucomatous eyes. Invest Ophthalmol Vis Sci. 2007;48:2099–104.
32. Tannenbaum D, Hoffman D, et al. Variable corneal compensation improves the discrimination between normal and glaucomatous eyes with the scanning laser polarimeter. Ophthalmology. 2004;111:259–64.
33. Toth M, Hollo G. Enhanced corneal compensation for scanning laser polarimetry on eyes with atypical polarisation pattern. Br J Ophthalmol. 2005;89(9): 1139–42.
34. Weinreb RN, Bowd C, et al. Measurement of the magnitude and axis of corneal polarization with scanning laser polarimetry. Arch Ophthalmol. 2002;120: 901–6.
35. Weinreb RN, Bowd C, et al. Glaucoma detection using scanning laser polarimetry with variable corneal polarization compensation. Arch Ophthalmol. 2003;121:218–24.

Optic Nerve: Optical Coherence Tomography

5

Bo Wang, Gadi Wollstein, and Joel S. Schuman

Core Messages

- The three-dimensional (3D) structure of the optic nerve head (ONH), the peripapillary thickness of the retinal nerve fiber layer (RNFL), and the ganglion cell complex (GCC) can be visualized objectively and assessed quantitatively with accuracy and precision using OCT.
- Quantitative measurements based on the 3D data set substantially enhance the diagnostic utility of ONH and macula scans.
- Spectral-domain (SD) OCT offers substantial advantages in terms of scanning speed and scanning quality compared to earlier generations OCT.

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5.1 What Indices Should I Use to Help Me Interpret the OCT Optic Nerve Head Analysis Report?

Since spectral-domain (SD) OCT was first introduced in early 2000, a number of manufacturers have unveiled their own commercial devices. Some of these devices were designed to primarily gather qualitatively high-quality images, with emphasis on visualization of retinal disease. Others devices were designed so that they are more quantitatively focused with extensive analysis software and rapid acquisition time. This chapter contains examples showing interpretation of some of the most commonly used commercial devices. However, the goal of this chapter is not to focus on a particular device, but to understand a set of broad principles that can be applied to all SD-OCT devices.

All current commercial SD-OCT devices offer the ability to assess the optic nerve head (ONH). All of them have a series of parameters focusing on various morphologic parameters of the disc, cup, and rim. The devices typically use a series of radial scans centered on the ONH or a cube scan. Radial scan pattern follows the scanning pattern performed with the earlier generation of OCT. While a radial scan pattern allows dense sampling at the crossing point of all scans in the center of the ONH, in the periphery the scans are spaced far apart and interpolation

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is used to fill in the missing information. A cube scan allows a consistent and thorough sampling of the entire area of interest, which permits additional post-processing analysis. Additionally, the cube scan often provides information from both the ONH and the peripapillary retinal nerve fiber layer (RNFL) in one scan. The ability to confirm structural changes in both ONH and peripapillary regions enhances diagnostic confidence.

The first step in assessing any OCT scan is to evaluate the image quality. The devices provide various global image quality parameters, such as signal strength and quality score, with their respective recommended ranges. Images of poor quality will result in poor segmentation of the structures of interest and lead to non-reliable results. Therefore, all manufacturers issue a signal cutoff with their device, below which the segmentation will be of questionable value. After assessing the signal quality, the next step is to determine whether the segmentation was adequate on the individual cross sections. For the ONH analysis, the interface between the vitreous and the ONH surface along with the retinal pigment epithelium should be properly delineated. Furthermore, Bruch's membrane opening, the termination of the retinal pigment epithelium, should be correctly marked as it delineates the ONH margin. The proper segmentation of these structures is paramount for all subsequent analysis and should be carefully assessed before making any clinical decision based upon the scans.

The disc margin on OCT is typically defined as the termination of the RPE layer, at Bruch's membrane opening, and reported quantitatively as the disc area. The location of the disc margin can be manually adjusted if the automated segmentation algorithm failed to locate it properly. The cup is defined by an offset parallel but anterior to a line drawn between the two opposing Bruch's membrane openings. The rim is defined as the area bounded anteriorly with the interface between the vitreous and the ONH and posteriorly with the offset line described above. The specific value of this offset is different between devices. However, it is important to remember that due to the way the disc and cup are computed in OCT, they may differ from the clinical assessment or from the assessment of fundus stereophotographs. These ONH parameters are compared with age-matched population-derived measurements and accordingly reported on a color-coded scale with green color denoting measurements within normal limits, yellow color indicating borderline or measurements appearing only in 1–5 % of the population, or red color denoting outside normal limits with a probability of less than 1 % to appear in the normal population. Some devices further stratify the normative data set so that it accounts for ethnicity in addition to age group.

A number of studies investigated the parameters that offer the best discrimination of glaucoma from healthy. These can be summarized using an area under receiver operating characteristic (AUC) curve, which shows both the sensitivity and specificity of the analysis. An AUC of 1 implies perfect discrimination, while an AUC of 0.5 approaches completely random discrimination. ONH parameters with high AUC in a number of studies include rim area and vertical cup-to-disc ratio.

Summary for the Clinician

- It is critical to assess both image quality and segmentation prior to interpreting results of OCT analysis.
- Most ONH analysis parameters depend on proper segmentation of Bruch's membrane opening and the interface between the vitreous and the ONH along with the inner limiting layer.
- The important ONH parameters for glaucoma diagnosis include rim area and vertical cup-to-disc ratio.

5.2 What Indices Should I Use to Help Me Interpret the SD-OCT RNFL Thickness Average Analysis Printout?

With the improved speed of SD-OCT, many devices are capable of assessing both the RNFL and ONH using the same scan pattern, providing a substantial scan time reduction from earlier generation OCT. For devices performing a cube scan, RNFL thickness is derived from sampling a 3.4 mm diameter circle centered on the ONH to create the "RNFL circular tomogram" shown in Fig. 5.1. The automated segmentation algorithm then identifies the ILM and the boundary between the brightly reflective RNFL and less reflective ganglion cell layer (GCL) below it. One advantage of extracting the circular RNFL from a cube scan is the ability to improve measurement reproducibility. The previous generation OCT, time-domain (TD-)OCT, had a relatively slow scanning speed and therefore sampling of the RNFL was acquired by a circular scan centered around the ONH. With TD-OCT decentration could be a problem, leading to falsely high or low RNFL measurements since RNFL is normally thicker when the scan circle is located closer to the ONH and thinner when it is farther from the ONH border. The ability to extract the RNFL thickness from the cube scan ensures proper centration of the circle and reduces measurement variability between visits from variations in the sampling circle location.

RNFL thickness measurement is compared to a population-derived database, allowing for detection of measurements deviating from the normal range. Parameters deviating from the age-matched normal range are labeled with the color-coded scale, as discussed in the previous section. Because the RNFL is lost as part of the natural process of aging, the comparison with an age-matched normative data is important to ensure the most sensitive means of detecting deviation from normal range. It should be noted that all OCT devices assume emmetropic eye length for the placement of the sampling circle. In a highly myopic eye, the sampling circle is projected further away from the beam origin than in an emmetropic eye, leading to a larger diameter projection in the eye. RNFL thickness further away from the ONH is thinner and therefore in highly myopic eyes the measured RNFL thickness might be reported as exaggeratedly thinner. Additionally, the normative database does not include children and therefore cannot be used for patients under the age of 18 years old.

The RNFL thickness profiles for both eyes are superimposed over the normative database information. The RNFL thickness is reported by an overall average thickness value, by quadrants, and by 12–16 sectoral measurements (varying between devices), which is shown in the printout in a wheel-like format. Once a clinician has insured optimal signal quality and segmentation, the sectoral, quadrant, and particularly the overall average RNFL thicknesses are the most clinically useful parameters. The RNFL thickness is also presented as a thickness profile along the sampling circle, where it has a typical "double hump" configuration. Thicker RNFL occurs at the superior and inferior poles of the optic nerve with thinner RNFL at the nasal and temporal sectors.

Summary for the Clinician

- It is important to assess both image quality and segmentation accuracy prior to interpreting results of OCT analysis.
- RNFL thickness is reported for sectors, quadrants, and as an overall average. The most useful RNFL parameters for glaucoma diagnosis are average RNFL thickness, superior and inferior quadrants RNFL thickness.

5.3 Can SD-OCT Detect Glaucomatous Progression?

It can be difficult to identify subtle glaucomatous changes over time, particularly if evaluation is based solely on fundus examination, without

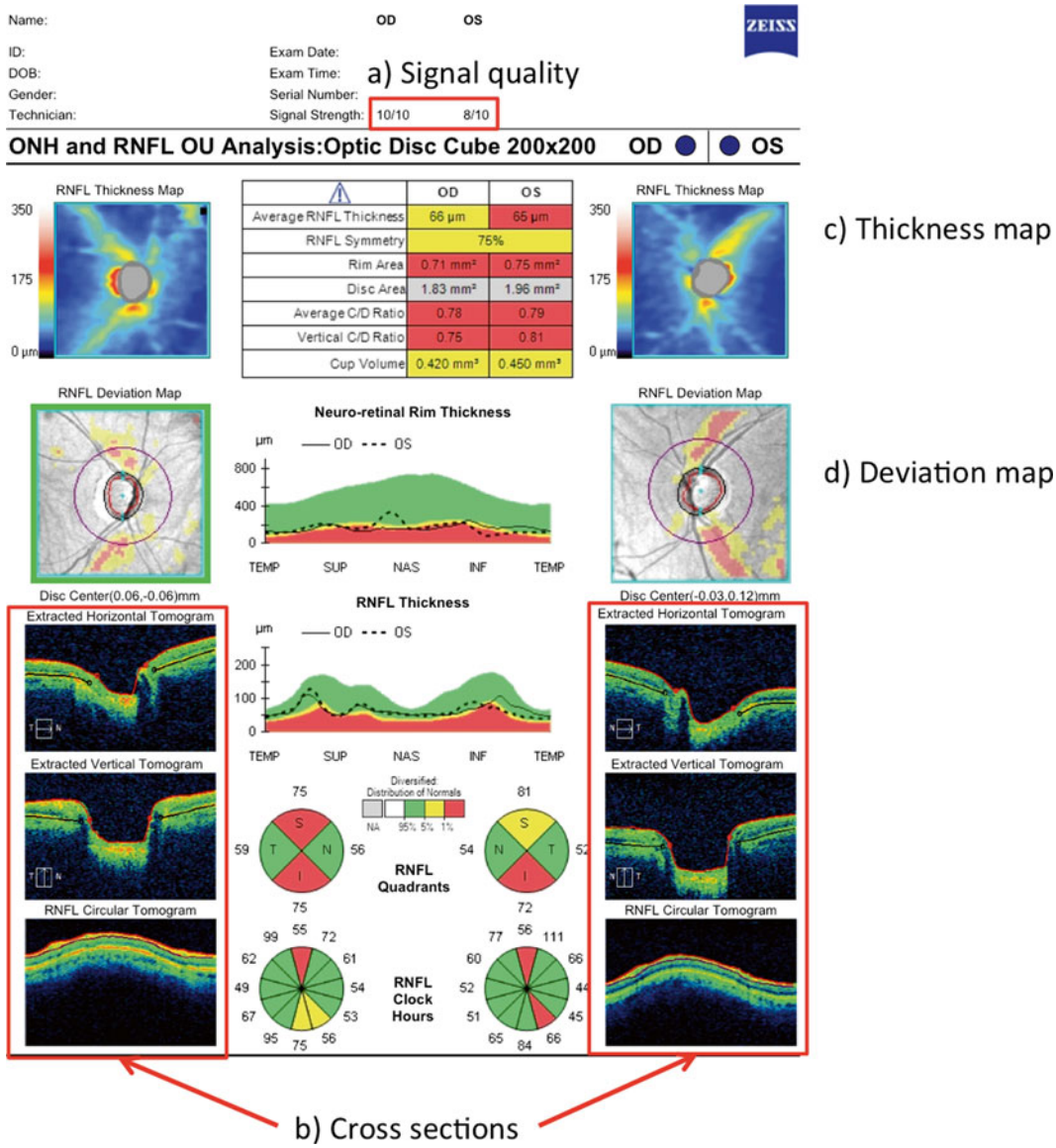

Fig. 5.1 Cirrus SD-OCT Optic Nerve Head Report. (**a**) Signal quality (reported as signal strength) from 0 to 10 (best). (**b**) Horizontal and vertical cross sections centered on the ONH, as well as the circular RNFL scan, which are all extracted from the 200 × 200 volume scan. The segmentation lines are overlain with the internal limiting membrane (*red*) and retinal pigment epithelium (*black*). (**c**) Color map of retinal nerve fiber layer thickness, with (**d**) the deviation from a normal healthy database. *Yellow color* indicates probability <5% in normal population while red indicates <1% probability

photo documentation. One of the greatest advantages of quantitative measurements is that they provide a more reliable metric than qualitative and subjective assessment of ONH appearance and surrounding nerve fiber layer to monitor change. This is a result of the high repeatability of SD-OCT measurements, which allow detection even of small changes in both the RNFL and ONH.

Glaucoma progression is typically performed by event-based or trend-based approaches. Event-based progression is detected when follow-up scans exceed a threshold of change based upon the measurements variability between baseline

tests. Trend-based progression analysis typically involves monitoring the progression using regression analysis. The patient is labeled as progressing when the slope of change in OCT parameter with time is significantly different from a no-change (zero) slope. Event-based analysis can sometimes identify progression before it is detected by trend-based analysis but is prone to erroneous measurements (outliers) appearing in situations such as poor quality scans. It is therefore recommended to repeat the test to confirm the event of progression. Trend analysis, which is less prone to outliers, requires a relatively large number of tests in order to provide reliable information.

Guided Progression Analysis (Fig. 5.2), the progression analysis report provided by Cirrus HD-OCT (Zeiss, Dublin, CA), illustrates an example of both methods of assessing progression. The top two image rows (Fig. 5.2a, b) illustrate an example of event-based progression. The RNFL thickness maps are registered to baseline images and locations where the RNFL thickness is below the threshold level, based on differences compared to the baseline visits, are color coded with the first occurrence of deviation colored in yellow and the second consecutive deviation at the same location colored in red. The graphs at the center of the printout (Fig. 5.2c) plot the RNFL thickness (average, super, and inferior quadrants) and cup-to-disc ratio versus patient's age. A significant progression is marked when the slope of change is significantly different from a zero slope.

A number of studies reported that both TD-OCT and SD-OCT are capable of documenting glaucomatous progression. However, while TD-OCT and SD-OCT have similar performance in glaucoma discrimination, SD-OCT has superior performance in determining glaucoma progression and a better agreement with visual field [1]. Finally, an important consideration for OCT progression analysis is for patients with advanced glaucoma. At a late stage of disease, OCT may be clinically less useful than visual field tests due to a "floor effect." Even with advanced loss, RNFL thickness will rarely drop below 40 μm, likely due to residual tissue and blood vessels. Therefore, SD-OCT progression analysis is best used in early to moderate stages of the disease, as well as for detection of pre-perimetric glaucoma.

Summary for the Clinician

- OCT is useful in the detection of glaucomatous progression. SD-OCT offers greater repeatability compared to TD-OCT, offering improved detection of glaucoma progression.
- Care must be taken to insure that all images chosen for progression analysis have good image and segmentation quality.
- OCT progression analysis may be more useful in early to moderate glaucoma, due to the floor effect on RNFL loss with advanced disease.

5.4 How Big of a Change Is Meaningful on the RNFL Analysis?

Numerous studies have established RNFL thickness and ONH parameters as excellent predictors of glaucoma. Most studies showed that ONH and RNFL analysis are comparable in terms of ability to discriminate between healthy and glaucoma [2]. However, there is no perfect agreement between the two regions and therefore, it is recommended to assess both the results of RNFL and ONH analysis, to get the best indication on a patient's current disease status. Global RNFL thickness, inferior quadrant, and superior quadrant RNFL thickness have been shown to provide the best diagnostic ability across studies. This has been true in early glaucoma (AUC = 0.75–0.96) [3, 4], as well as in more moderate levels of glaucoma, with AUC of 0.78–0.94 for the overall, superior, and inferior quadrant RNFL thickness values [5, 6]. Of these three parameters, there was not a consistent best performer, so it is advised that one examines all three of these parameters when making clinical assessments [5, 6].

A meaningful guideline for change can be inferred from the variability of the RNFL and ONH parameter results when scanning is repeated within a short period of time. Within a short

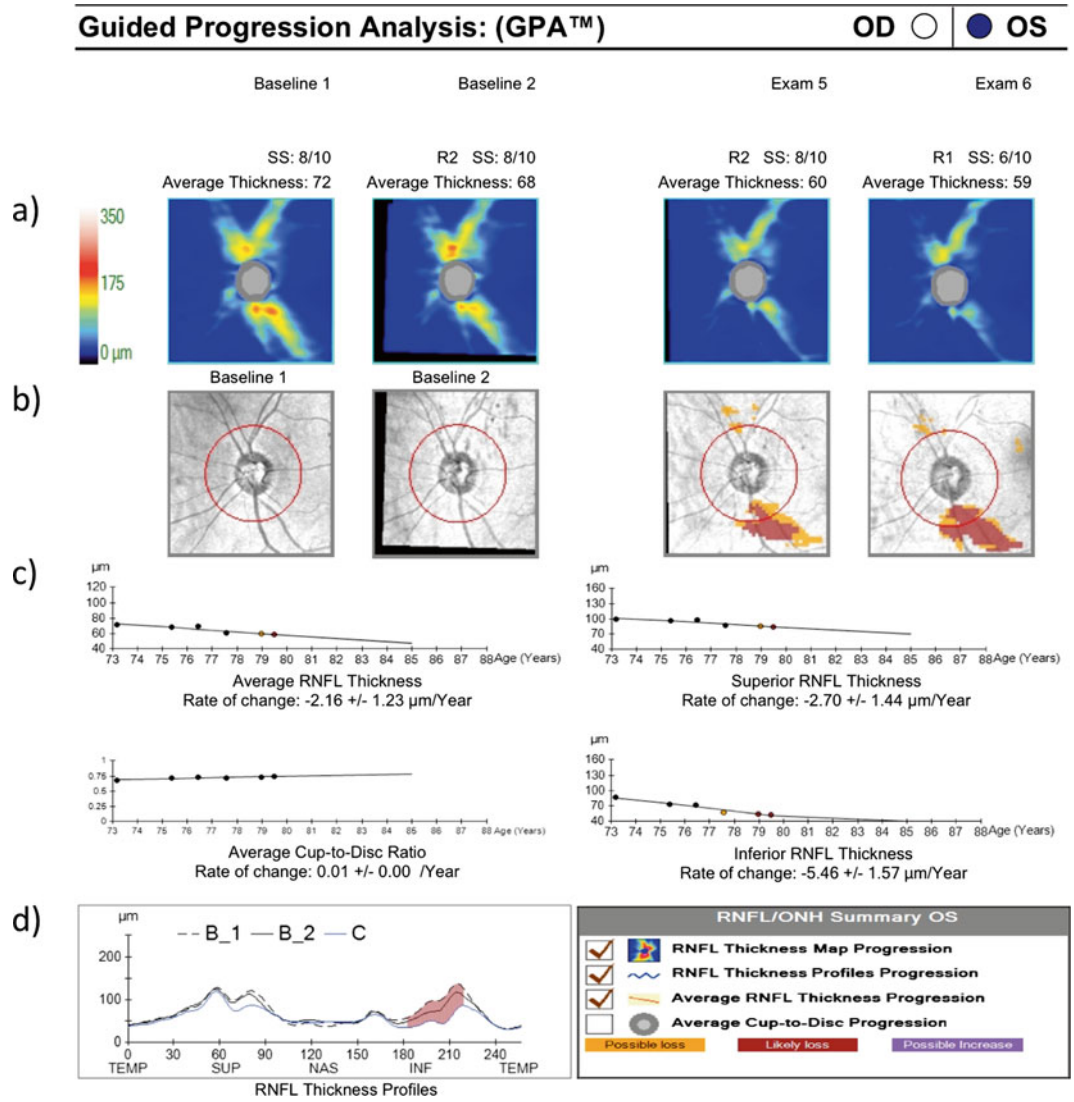

Fig. 5.2 Cirrus HD-OCT guided progression analysis report. (**a**) RNFL thickness maps from baseline and the most recent visits. (**b**) Fundus images color coded to denote a significant change from baseline (*orange*—one significant deviation from baseline, *light brown*—consecutive deviations from baseline). (**c**) Plot of average RNFL thickness, superior and inferior RNFL thickness, and cup-to-disc ratio over time. Time points where the rate of change was statistically significant are marked with the same color code conventions. (**d**) Thickness profile along the peripapillary circle where clusters of points deviate from baseline thickness are marked in *red*

period of time (i.e., tests repeated on the same day), true structural changes are not expected to occur. Any change in the parameters is due to the inherent variability in the system's measurements and should not be considered meaningful. Therefore, any change that exceeds the device's inherent variability should be considered as a meaningful change.

The above Tables 5.1 and 5.2 show the coefficient of variation for both ONH and RNFL analyses. The coefficient of variation represents the inherent percent variability in the system. If the patient experiences a percent change in their RNFL or ONH parameter greater than the coefficient of variation, the clinician should suspect disease progression.

Table 5.1 ONH parameters coefficient of variation from Mwanza et al. [7]

Parameter	Coefficient of variations (%)
Disc area (mm^2)	4.4
Rim area (mm^2)	6.6
Cup volume (mm^3)	5.9
Cup/disc area ratio	1.1
Cup/disc horizontal ratio	2.2
Cup/disc vertical ratio	1.7
Horizontal rim thickness (μm)	6.7
Vertical rim thickness (μm)	7.6

Table 5.2 RNFL parameters coefficient of variation from Mwanza et al. [7]

Parameter (μm)	Coefficient of variations (%)
Overall mean	1.9
Superior	3.2
Inferior	3.7
Nasal	4.8
Temporal	4.6
12 o'clock	4.6
1 o'clock	5.6
2 o'clock	4.3
3 o'clock	10.0
4 o'clock	4.9
5 o'clock	4.2
6 o'clock	6.0
7 o'clock	4.9
8 o'clock	6.4
9 o'clock	6.0
10 o'clock	5.5
11 o'clock	5.6

Furthermore, besides for the absolute RNFL value, an important source of assessing the RNFL also involves the RNFL thickness deviation map. This map can highlight localized defects that sometimes are located outside the 3.4 mm diameter sampling circle with the typical wedge defect configuration that are due to glaucomatous damage and otherwise would have been missed by the quantitative RNFL thickness global parameters [8]. It is therefore recommended to routinely assess the deviation map for the presence of localized defects in addition to the assessment of the RNFL thickness measurements.

Summary for the Clinician

- Changes in OCT measurements recorded over time that exceed the inherent device variability should be considered as a true indication of structural progression.

5.5 How Can Ganglion Cell Complex (GCC analysis) Help with the Management of Glaucoma?

While glaucoma is associated with retinal ganglion cell (RGC) damage, traditional methods of diagnosing the disease using OCT only assess this loss indirectly, via the RNFL. Direct visualization and quantification of the RGC layer reduces the confounding effect of outer retinal layers that might mask the glaucomatous damage when the full retinal thickness is measured. The main challenge is related to the RGC layer being a low reflectance layer, which appears as a dark band in OCT images. Therefore, since the early days of OCT, RNFL thickness, which quantifies the thickness of the RGC's axons, has been used as the primary method for indirectly assessing the RGC health. Commercial SD-OCT devices can provide reliable and reproducible imaging of the RGCs and adjacent layers. However, measurement of the GCL alone is extremely difficult, due to the similar reflectivity of the GCL and the IPL. Most GCC analysis quantifies the inner retinal layers, composed of the nerve fiber layer (RGC axons), ganglion cell layer (RGC cell body), and inner plexiform layer (RGC dendrites). In some devices, the RNFL layer is excluded and the ensuing parameter is called GC-IPL.

The segmentation of the macula is used to create a topographic map of GCC thickness, with the center of the map around the fovea. The characteristic configuration of the GCC map demonstrates a donut or C-shaped thickening of the GCC just outside of the fovea. Furthermore, the GCC thickness is compared to population-derived age-matched data to allow detection of

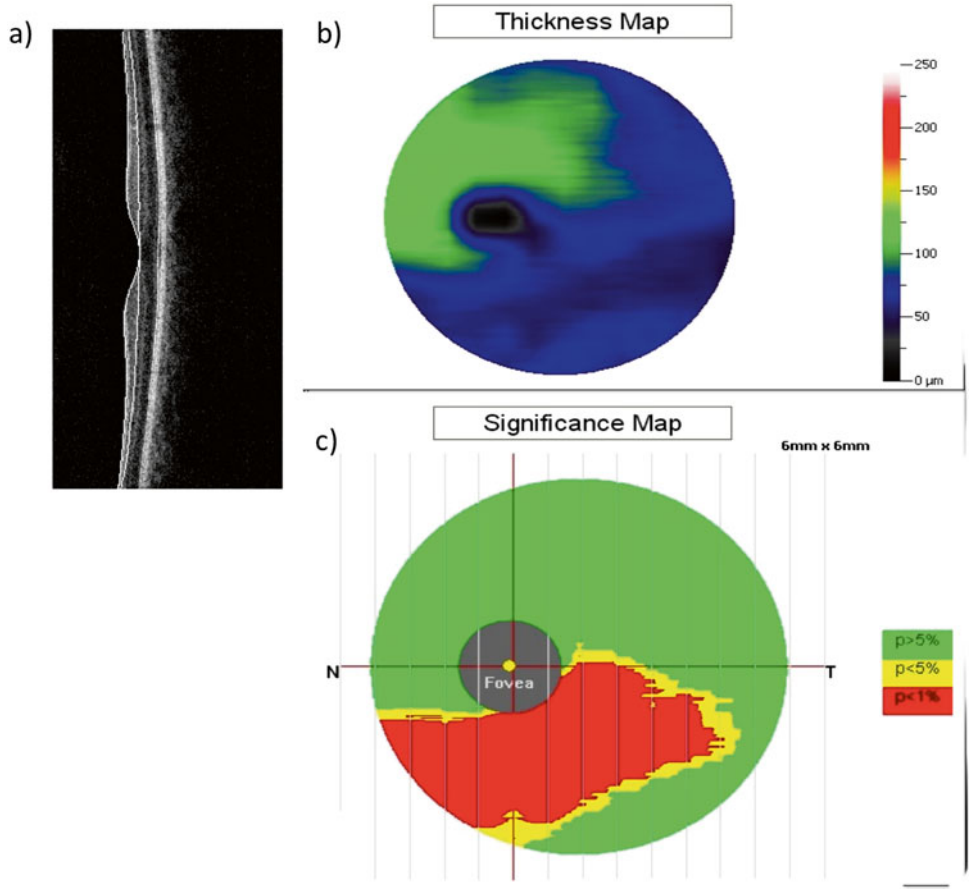

Fig. 5.3 RTVue Ganglion Cell Analysis report. (**a**) Cross-sectional scan of the macula region with the segmentation of the GCC. (**b**) Color-coded thickness map of the GCC. (**c**) Color-coded map of the macula based on significant difference from population-derived GCC thickness. *Yellow color* indicates probability <5% in normal population while red indicates <1% probability

area deviating from the normal range. Some manufacturers divide the macula into squares, while others divide it into the traditional pie-shaped sectors. The results are summarized much the same way as RNFL, with green regions denoting within normal limits, yellow regions denoting borderline region ($p<0.05$), and red outside normal limits ($p<0.01$).

While GCC is no better than circumpapillary RNFL for glaucoma discrimination, it offers another tool to assess glaucoma damage [9]. It is important to note that unlike RNFL assessment, which assesses all the RGC axons of the retina, GCC is only capable of assessing the RGCs within the macula, encompassing approximately 50 % of the retina ganglion cells. Thinning of GCC and GCL-IPL were shown to occur in glaucoma and in pre-perimetric stages of the disease [9, 10]. GCC may also be a useful parameter for detecting structural progression. Lower GCC at baseline may be at higher risk for progression compared to subjects with a high GCC, with average thickness as well as global volume loss being significant variables [11]. The presence of glaucomatous damage or structural progression in the macula that corresponds with abnormality in the peripapillary region or ONH strengthens the clinical confidence about the accuracy of the glaucomatous findings.

Table 5.3 GCC parameters covariance from Mwanza et al. [14]

Parameter (GCC thickness)	Coefficient of variations (%)
Average	1.8
Minimum	4.2
Superotemporal	3
Superior	2.2
Superonasal	2.7
Inferonasal	3.1
Inferior	3.6
Inferotemporal	2.5

Clinician Summary

- GCC, composed of the macular RNFL, GCL, and inner plexiform layer, can be used to detect ganglion cell loss in the macula.
- GC-IPL includes only the GCL and the inner plexiform layer.
- The discriminatory power of GCC and GC-IPL is similar to RNFL.

5.6 How Big a Change Is Meaningful on the GCC Analysis?

Numerous studies have shown that GCC and GC-IPL are powerful parameters to assess glaucoma. The diagnostic accuracy of GCC and GC-IPL are comparable to that of both ONH and RNFL analysis [12, 13]. The best GCC parameters include minimum, inferotemporal, and average GCC thickness [12]. The most comprehensive evaluation of a glaucoma patient should involve all three analyses: ONH, RNFL, and GCC.

A meaningful change is based on the expected inter-visit repeatability to determine the expected variation (Table 5.3).

A common trend for GCC, RNFL, and ONH parameters is that global parameters tend to be the most reproducible, demonstrating the lowest coefficient of variation. This is because global parameters summarize larger regions and are consequently less noisy. The coefficient of variation represents the inherent percent variation in the thickness measurements. Therefore, any percentage change in GCC greater than the listed value in Table 5.3 should be suspicious for a glaucomatous change.

Summary for the Clinician

- Changes in GCC or GC-IPL measurements recorded over time that exceed the inherent device variability should be considered as a true indication of structural progression.

5.7 If I Have a Time-Domain OCT in My Practice, Is It Below Standard of Care at This Time?

TD-OCT has limitations of both axial resolution and scanning speed that affect image detail quality and leave it vulnerable to eye motion artifacts. New advances in SD-OCT reduce these limitations significantly. SD-OCT greatly improves scanning speed, scanning about 40–130 times faster, depending on the device. This increased scanning speed allows the acquisition of a complete 3D raster scan over the ONH (Fig. 5.4). The 3D volume permits the visualization of all ONH details by construction of the OCT fundus image representing the total reflectance at each axial scan point, created from averaging along each axial scan to produce a 2D image of the retinal and ONH surface. Volume imaging also facilitates the identification and correction of motion artifact. The SD-OCT fundus image resembles a photograph of the retina (Fig. 5.4), but unlike a photograph, it can also be resolved in 3D. The SD-OCT volume allows ONH and RNFL parameter measurement without the need for interpolation, which provide a more accurate and precise assessment of the disc. Finally, one important advantage of acquiring the entire 3D volume is that ONH and RNFL assessment can now be done using only one scan, instead of two.

While SD-OCT offers significant advantages compared to TD-OCT, numerous studies have

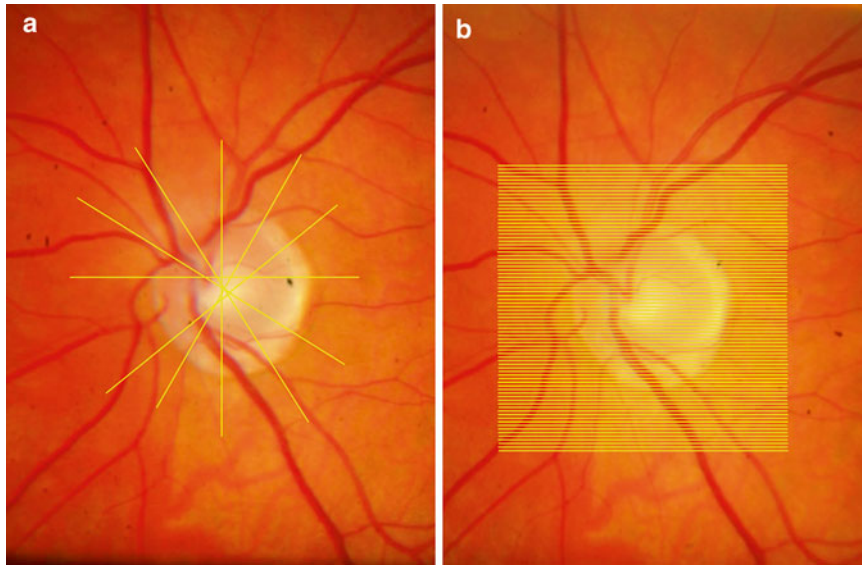

Fig. 5.4 Comparison of TD-OCT and spectral-domain OCT ONH scan patterns. *Yellow lines* indicate where OCT data is sampled. (**a**) Misalignment of TD-OCT radial scan lines due to eye movement during scan acquisition causes decentration of individual lines. Another disadvantage of this scan pattern is that data must be interpolated between the lines. (**b**) SD-OCT raster scan lines cover a 3D volume, allowing for scan alignment and eliminating the need for interpolation

determined that they have similar ability to discriminate between healthy and glaucoma [15, 16]. This suggests that at least for the initial assessment of a new patient, there is no difference between the two modalities. By assessing the RNFL within a cube volume, SD-OCT permits more reliable and repeatable assessment of RNFL thickness. With TD-OCT, motion of the eye makes it impossible to know exactly where in the tissue the circle scan data was obtained as eye motion can cause decentration of the circle scan with respect to the ONH. With a 3D data set, a correctly centered RNFL circle can be selected automatically in post-processing to allow for accurate circle centration on the ONH. This also makes it possible to ensure that data are obtained at the exact same location for each subsequent scan. These advantages lead to increased repeatability for SD-OCT. These qualities make SD-OCT advantageous compared with TD-OCT for glaucoma progression detection.

Currently, there are a number of SD-OCT devices available commercially for clinical use, each with their own advantages and disadvantages. Some devices are more focused on gathering high-quality images for qualitative analysis, with emphasis on visualization of retinal disease and flexibility in scan pattern acquisition. Others are more quantitatively focused with extensive analysis software for measuring parameters. Identifying the most appropriate OCT device depend on the specific needs of any given practice.

Summary for the Clinician

- SD-OCT technology has better depth resolution and faster scanning speeds than TD-OCT.
- SD-OCT allows for measurement of the ONH without interpolation between scans and allows placement of RNFL circles via automated post-processing—which is possible because of the faster scanning speed of SD-OCT allows the acquisition of a 3D data cube that can be sampled post hoc.

- While SD-OCT does not improve glaucoma detection when assessing RNFL alone, it allows (1) more reliable follow-up visits to assess progression, (2) reduced scan time, and (3) improved functionality in a multi-specialty practice.

References

1. Leung CK-S, Chiu V, Weinreb RN, Liu S, Ye C, Yu M, Cheung CY, Lai G, Lam DS-C. Evaluation of retinal nerve fiber layer progression in glaucoma. Ophthalmology. 2011;118(8):1558–62.
2. Mwanza J-C, Oakley JD, Budenz DL, Anderson DR. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. Ophthalmology. 2011;118(2):241–8.e1.
3. Badalà F, Nouri-Mahdavi K, Raoof DA, Leeprechanon N, Law SK, Caprioli J. Optic disk and nerve fiber layer imaging to detect glaucoma. Am J Ophthalmol. 2007;144(5):724–32.
4. Nouri-Mahdavi K, Nikkhou K, Hoffman DC, Law SK, Caprioli J. Detection of early glaucoma with optical coherence tomography (stratus OCT). J Glaucoma. 2008;17(3):183–8.
5. Wollstein G, Ishikawa H, Wang J, Beaton SA, Schuman JS. Comparison of three optical coherence tomography scanning areas for detection of glaucomatous damage. Am J Ophthalmol. 2005;139(1):39–43.
6. Anton A, Moreno-Montañes J, Blázquez F, Alvarez A, Martín B, Molina B. Usefulness of optical coherence tomography parameters of the optic disc and the retinal nerve fiber layer to differentiate glaucomatous, ocular hypertensive, and normal eyes. J Glaucoma. 2007;16(1):1–8.
7. Mwanza J-C, Chang RT, Budenz DL, Durbin MK, Gendy MG, Shi W, Feuer WJ. Reproducibility of peripapillary retinal nerve fiber layer thickness and optic nerve head parameters measured with cirrus HD-OCT in glaucomatous eyes. Invest Ophthalmol Vis Sci. 2010;51(11):5724–30.
8. Jeoung JW, Park KH. Comparison of cirrus OCT and stratus OCT on the ability to detect localized retinal nerve fiber layer defects in preperimetric glaucoma. Invest Ophthalmol Vis Sci. 2009;51(2):938–45.
9. Tan O, Chopra V, Lu AT-H, Schuman JS, Ishikawa H, Wollstein G, Varma R, Huang D. Detection of macular ganglion cell loss in glaucoma by fourier-domain optical coherence tomography. Ophthalmology. 2009;116(12):2305–14.
10. Nakano N, Hangai M, Nakanishi H, Mori S, Nukada M, Kotera Y, Ikeda HO, Nakamura H, Nonaka A, Yoshimura N. Macular ganglion cell layer imaging in preperimetric glaucoma with speckle noise-reduced spectral domain optical coherence tomography. Ophthalmology. 2011;118(12):2414–26.
11. Anraku A, Enomoto N, Takeyama A, Ito H, Tomita G. Baseline thickness of macular ganglion cell complex predicts progression of visual field loss. Graefes Arch Clin Exp Ophthalmol. 2014;252(1):109–15.
12. Mwanza J-C, Durbin MK, Budenz DL, Sayyad FE, Chang RT, Neelakantan A, Godfrey DG, Carter R, Crandall AS. Glaucoma diagnostic accuracy of ganglion cell-inner plexiform layer thickness: comparison with nerve fiber layer and optic nerve head. Ophthalmology. 2012;119(6):1151–8.
13. Schulze A, Lamparter J, Pfeiffer N, Berisha F, Schmidtmann I, Hoffmann EM. Diagnostic ability of retinal ganglion cell complex, retinal nerve fiber layer, and optic nerve head measurements by Fourier-domain optical coherence tomography. Graefes Arch Clin Exp Ophthalmol. 2011;249(7):1039–45.
14. Mwanza J-C, Oakley JD, Budenz DL, Chang RT, Knight OJ, Feuer WJ. Macular ganglion cell-inner plexiform layer: automated detection and thickness reproducibility with spectral domain-optical coherence tomography in glaucoma. Invest Ophthalmol Vis Sci. 2011;52(11):8323–9.
15. Chang RT, Knight OJ, Feuer WJ, Budenz DL. Sensitivity and specificity of time-domain versus spectral-domain optical coherence tomography in diagnosing early to moderate glaucoma. Ophthalmology. 2009;116(12):2294–9.
16. Schuman JS. Spectral domain optical coherence tomography for glaucoma (an AOS thesis). Trans Am Ophthalmol Soc. 2008;106:426–58.

Optic Nerve Head and RNFL Imaging: Comparison of Technologies

6

Kouros Nouri-Mahdavi, Carlos Souza, and Joseph Caprioli

Core Messages

- Each optic nerve imaging technology has its unique strengths and weaknesses.
- Spectral-domain OCT is rapidly becoming the device of choice for detection of glaucoma and is promising for disease monitoring due to its widespread availability, high resolution, facility of use, ability to image multiple areas of the fundus, and excellent reproducibility.
- Frequency of imaging should be determined taking into account factors such as stage of glaucoma, intraocular pressure control, or suspicion of disease deterioration.

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6.1 Why Image the Optic Nerve?

Optic disc evaluation is of the utmost importance in early glaucoma diagnosis and in monitoring progressive optic nerve damage. Optic disc and retinal nerve fiber layer (RNFL) abnormalities can often precede corresponding functional loss in glaucoma [1–3]. Therefore, it is imperative to have an objective, quantitative, and reproducible imaging technique capable of making an early diagnosis and monitoring the disease.

There are many imaging techniques available for optic disc and RNFL evaluation in glaucoma. Confocal scanning laser ophthalmoscopy (HRT; Heidelberg Retina Tomography; Heidelberg Engineering, Heidelberg, Germany), scanning laser polarimetry (GDx; Carl Zeiss Meditec, Dublin, California, USA), and more recently optical coherence tomography are widely used by glaucoma specialists, although the mainstay of clinical practice remains subjective optic disc evaluation with stereoscopic optic disc photography. There is enough data in the literature to support the use of imaging technology as a complementary tool to clinical evaluation in glaucoma diagnosis and monitoring [4–10]. All imaging technologies have their inherent advantages and limitations. The available data in the literature suggest that objective imaging technologies can approach the performance of subjective assessment of stereo optic disc photographs by experts with regard to identifying early

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glaucoma [4, 5, 11]. However, imaging technologies have the following advantages: (1) they provide objective and quantitative measurements of the optic disc and RNFL and (2) there is less variability between observers when examining data provided by the devices.

6.1.1 As Compared to the Other Imaging Technologies, What Are the Main Advantages and Disadvantages of Confocal Scanning Laser Ophthalmoscopy (HRT)?

The HRT is a confocal scanning laser ophthalmoscope with high axial optical resolution (up to about 30 μm) that uses a diode laser (670 nm wavelength) to sequentially scan the retinal surface at multiple focal planes.

The HRT has been available since the early 1990s and despite many modifications the platform has remained stable so that images taken with later iterations of the device can be compared to older images. In addition, until very recently, HRT was the only available automated imaging system for the optic disc providing both global and regional data. Through the years, the HRT's software has also undergone significant improvements with regard to both detection of glaucoma and its progression. The confocal scanning laser ophthalmoscope is currently in its third generation. The HRT-3 software features improvements in image scaling and alignment, a new diagnostic classification system, and an expanded normative database. The new shape-based analysis (the Glaucoma Probability Score) does not require an examiner to draw a contour line around the optic disc, which decreases the inter-operator variability, and it is independent of a reference plane position [6, 13]. The HRT-3 software has a larger ethnicity-specific normative database that also adjusts for optic disc size and age-related changes in the optic disc, with perhaps a higher accuracy in the analyses provided by the instrument [12]. The new scaling and alignment algorithm improve the ability to measure stereometric parameters such as area and volume-based measurements, height variation contour, and RNFL cross-sectional area. They also improve the progression analyses [8, 14]. The HRT-3 has an advantage over other imaging technologies in that it is compatible with the earlier software versions of the device (HRT-2 and HRT-1), and therefore it is possible to compare HRT-3 images with images taken with prior versions of the instrument. This allows glaucoma progression to be detected over a much longer period of time, which is a real advantage in longitudinal studies (Fig. 6.1) [8].

Both clinical disc exam and HRT measure what is now known as the horizontal neuroretinal rim width (HRW) [15]. Recent work has shown that such measurements do not always correctly reflect the remaining axonal complement of the optic nerve [16, 17]. Also, significant variability is introduced into rim measurements depending on the degree of optic disc tilt. Most studies that have explored the agreement of HRT with optic disc evaluation or visual field measurements for detection of progression have shown poor agreement with the former, the source of which is not quite clear [18, 19]. HRT measurements are also subject to blurring by media opacity and image quality suffers significantly under such circumstances. Other limitations of HRT include inability to detect disc hemorrhages (this is a shortcoming of all imaging devices), low reproducibility with high refractive errors, and performance variability as a function of the optic disc size. Studies have demonstrated good reproducibility between different operators; however, clinically significant inter-operator variations do exist because of the differences in how individuals draw the contour line around the optic nerve in older versions [13, 20]. The HRT measurements rely heavily on how the reference plane is defined. Many reference planes have been defined over the years and none have been proven to be optimal [21].

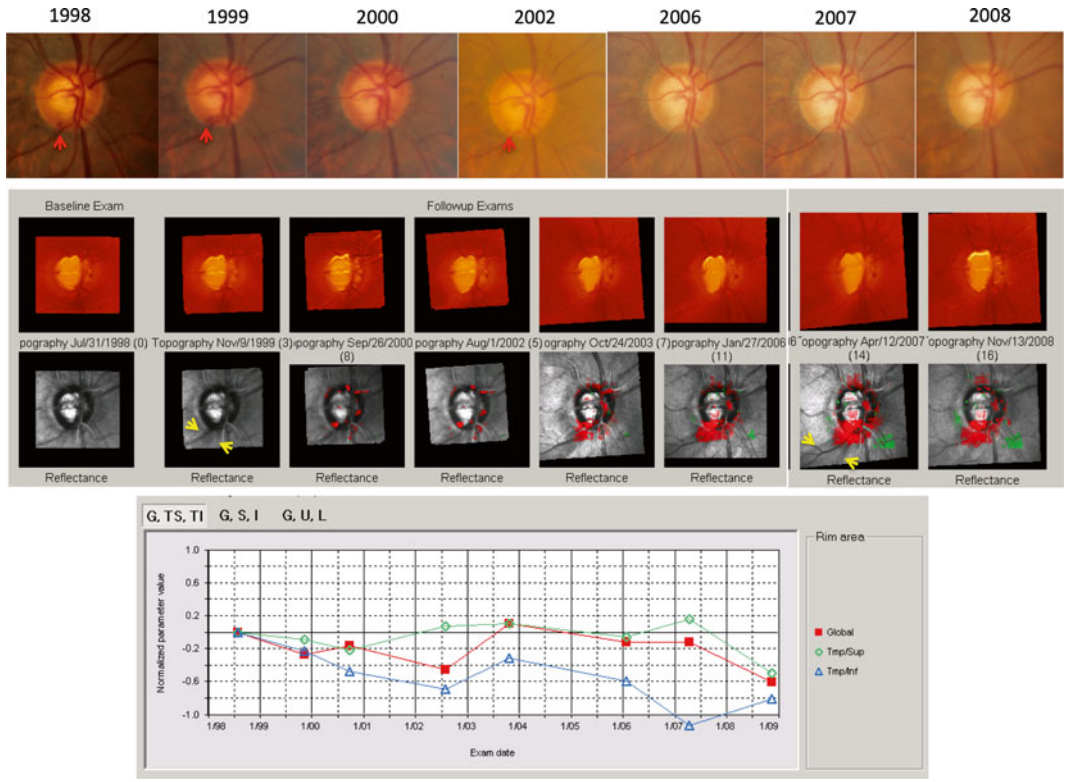

Fig. 6.1 A series of disc photographs (*top row*) and HRT images (*middle row*) spanning 10 years of follow-up. Both demonstrate significant progressive thinning of the neuroretinal rim inferiorly. Areas marked in *red* on HRT's reflectance images depict regions where progressive rim thinning has occurred. Multiple disc hemorrhages (*red arrowheads*) can be observed on disc photographs and enlargement of a retinal nerve fiber layer wedge defect inferiorly (*yellow arrowheads*) can also be seen on HRT's reflectance images. *Bottom row*: Series of trend analyses on normalized neuroretinal rim parameters demonstrate worsening of the inferior temporal rim (*blue line* and *glyphs*) while a change in global (*red line* and *glyphs*) and superotemporal rim (*green line* and *glyphs*) is less obvious

6.1.2 As Compared to the Other Imaging Technologies, What Are the Main Advantages of Optic Optical Coherence Tomography?

Optical coherence tomography is a high-resolution imaging technique based on the principle of low-coherence interferometry. It is capable of providing cross-sectional images of ocular structures [10, 22–24]. The device works by measuring the time delay difference between laser light reflected at various retinal layers and a reflected reference beam. The third generation of time-domain OCT (TD-OCT, Stratus OCT, Carl Zeiss Meditec, Inc.) has now been largely replaced by spectral-domain or Fourier-domain OCTs (SD-OCT). The latter use a spectrometer to simultaneous measure multiple A-scans reflected from the eye, and therefore are much faster than the time-domain technology (about 25,000–50,000 A-scans per second). The axial resolution of current generation SD-OCTs is about 3–5 μm. As a result, a much larger area of the peripapillary or macular retina can be measured (seen in measurement cubes).

The SD-OCTs are able to scan the peripapillary retina (RNFL scan), the optic nerve head (ONH), and the macular region in a short time span. They therefore provide multilevel imaging, which is a unique feature of the SD-OCTs (Fig. 6.2). At the same time, because of the very high speed of imaging with SD-OCTs, a huge amount of data is engendered by the devices that

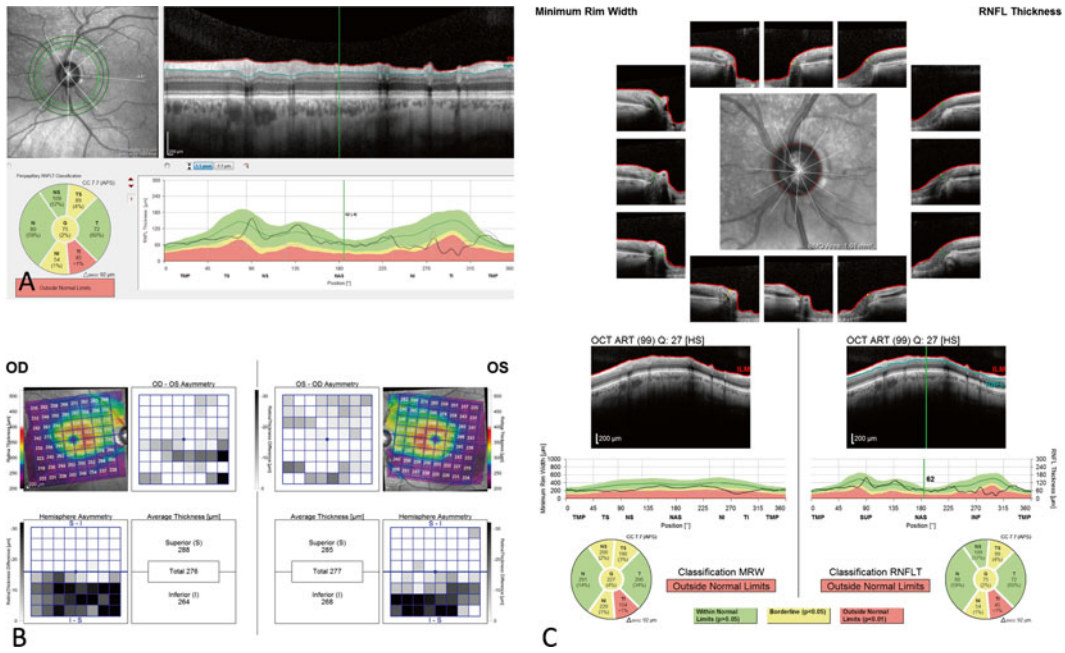

Fig. 6.2 Multilevel imaging with spectral-domain optical coherence tomography. (**a**) *Top*, three measurement circles where RNFL thickness is measured on Spectralis SD-OCT with respect to the center of Bruch's membrane opening; *bottom left*, RNFL thickness measurements in OCT sectors with corresponding percentile levels and color scales (*green*: within normal limits, *yellow*: measurement between 1 and 5 % of the distribution in the normative database; *red*: measurement falls below the 1 % of the values in the normative database); *bottom right*, the TSNIT curve from the current exam (*black curve*) and comparison to the prior exam (fainter gray curve). (**b**) Macular asymmetry printout from Spectralis SD-OCT. The thickness measurements in the central 24×24 degrees of the measurement cube are provided in an array of 8×8 cells. The numbers represent full macular thickness values although the newer version of the software is able to provide thickness measurements in individual layers. (**c**) The optic disc printout of the same device demonstrating: on *top*, the localization of the inner edge of the Bruch's membrane and segmentation of the internal limiting membrane along 12 radial B-scans; *middle*, the raw images for the RNFL scans; *bottom left*, the sectoral rim measurements with corresponding percentile levels and color scales; *bottom right*, sectoral RNFL measurements with corresponding percentile levels and color scales

can be used by clinicians to make decisions with regard to diagnosis of glaucoma or stability of the disease. The software and hardware for SD-OCTs are being improved upon constantly. This has created instability in the software and platforms, and hence comparison of images taken a few years apart can be problematic. It is now clear that images obtained with one SD-OCT machine cannot be directly compared to those from another device and that measurements from SD-OCTs cannot be directly compared to those of TD-OCTs [25–27].

Several studies confirmed that SD-OCT RNFL thickness measurements are useful to distinguish mild-to-moderate glaucoma patients from healthy subjects, with reasonable sensitivity at high specificities [28–30]. ONH algorithms are less well developed on SD-OCTs, and most devices provide global parameters for the ONH [31]. New approaches defining an optimal neuroretinal rim parameter (minimum rim width) have been reported, and it is expected that related software will be approved by the FDA to address this shortcoming of SD-OCTs [32]. However, global ONH parameters, most commonly vertical cup-to-disc ratio, have been found to be good performers for discrimination of patients with perimetric or preperimetric glaucoma from normal subjects [29, 31, 33]. Given the choice of the SD-OCT wavelength (in the 800s), media opacity is less of an issue with these devices compared with HRT. OCT has also demonstrated the

strongest structure–function correlation of all imaging techniques [34–37]. There are many studies demonstrating the reproducibility of RNFL, ONH, and macular thickness measurements with SD-OCTs [38–42]. These findings have significant implications with regard to detection of progression using SD-OCTs, and initial reports seem promising. Some SD-OCTs have software that provides clinicians with a statistical analysis program (GPA) to facilitate the detection of progression by comparing the RNFL thickness over time.

6.1.3 As Compared to the Other Imaging Technologies, What Are the Main Advantages of Scanning Laser Polarimetry?

Scanning laser polarimetry (SLP) is a technique used to evaluate the peripapillary RNFL thickness based on the birefringent properties of the retinal nerve fibers attributed to the microtubules in RNFL [43]. A change in retardation of polarized light is seen in proportion to axonal or RNFL thickness [44]. Birefringence is described in terms of polarization axis and polarization magnitude. In the anterior segment, the cornea and lens are also birefringent and may affect the measurements.

The commercial version of SLP, called GDx, is equipped with an enhanced corneal compensation mechanism (GDx-ECC) that allows eye-specific compensation of anterior segment birefringence and improves the signal-to-noise ratio of measurements by reducing atypical retardation patterns. Atypical retardation patterns may be present in 15–51 % of glaucomatous eyes [9, 45], and are more frequently observed in older subjects and in high myopia. The ECC algorithm enhances the signal-to-noise ratio by extracting the retinal retardation mathematically from the total retardation of the images [46]. The ECC algorithm has increased the ability of SLP to discriminate between healthy and glaucomatous patients, especially in those cases with high atypical retardation patterns and moderate to high myopia [9, 44, 46]. Studies show that the SLP-ECC is at least as reproducible as the prior iteration of SLP (GDx-VCC) [44–46]. The former has also improved the correlation between visual function and RNFL measures. The best parameter on the GDx device for discriminating glaucomatous from normal eyes is the nerve fiber indicator (NFI)—a global parameter derived from a support vector machine algorithm.

Since the advent of the SD-OCTs, SLP has rapidly lost its popularity since it solely measures the peripapillary RNFL and due to the fact that atypical retardations are a frequent and significant source of noise that are not observed with SD-OCTs. Another limitation of the SLP is that newer versions are not compatible with older versions of the instrument, making it difficult to carry on a longitudinal evaluation for detection of glaucoma progression.

Summary for the Clinician

- Evaluation of the optic disc and peripapillary RNFL is a most valuable tool for making a diagnosis of early glaucoma, and therefore, quantitative measurement of these structures is highly desirable.
  - All imaging technologies are highly reproducible and show good correlation with disc photographs and functional tests.
  - All imaging technologies are excellent complementary tools in the diagnosis and monitoring of glaucoma.
- The newest generation of confocal scanning laser ophthalmoscope (HRT) has improved image scaling and alignment, provides a new classification system, and contains an expanded normative database that includes various ethnicities. Its greatest strength is that the newest software is compatible with the previous versions enabling it to longitudinally study the optic disc over time.
- HRT has demonstrated some utility for detection and quantification of glaucoma progression.

- At the present time, SD-OCT devices have become the standard approach for detection of early glaucomatous damage at the level of the RNFL, optic disc, or macula and are most promising for the early detection of glaucoma.
- Optical coherence tomography RNFL thickness measurements provide the strongest structure–function relationships among all imaging devices. The normative database does not include ethnicity at this point in time and measurements may be affected by high refractive error and media opacity.
- Scanning laser polarimetry estimates the RNFL thickness, and the new measurement algorithm (ECC) has improved the signal-to-noise ratio and correction for anterior segment birefringence over previous versions. However, the latest version of GDx (GDx-Pro) is no longer commercially available.

6.2 How Often Should I Image the Nerve?

This is a difficult question to answer. The advent of imaging devices has made it possible to assess the optic nerve objectively whenever the ophthalmologist thinks it is necessary to do so [6, 8–10, 47]. However, there is no one size fits all strategy on how often the nerve should be imaged because there are many variables that must be considered in deciding when to image. Each individual patient will have different circumstances that dictate a different frequency of imaging, and therefore it is impossible to make a statement on frequency that will be right for every patient. For example, the optic disc of a low-risk ocular hypertensive subject may be imaged annually, whereas the optic disc of a patient with established glaucoma might need to be imaged every 3–6 months. A patient should be categorized into the appropriate risk group (does the patient have early, moderate, or advanced glaucoma, is the patient progressing) before deciding how often the optic disc must be imaged. Of note, both the RNFL and the optic disc will commonly demonstrate severe damage by the time the visual field has reached a mean deviation of −10 to −12 dB [48]. In such eyes, detection of progression is very difficult if not impossible; however, there is some indication that macular SD-OCT imaging may be helpful in these eyes [24, 49].

Summary for the Clinician

- Varying frequencies of imaging is indicated in different patients.
- In ocular hypertensives or glaucoma suspects imaging once yearly is probably adequate.
- In uncontrolled or progressing glaucoma, imaging can be justified every 3–6 months to look for change.

References

1. Sommer A, Miller NR, Pollack I, Maumenee AE, George T. The nerve fiber layer in the diagnosis of glaucoma. Arch Ophthalmol. 1977;95(12:2149–56.
2. Quigley HA, Addicks EM, Green WR. Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch Ophthalmol. 1982;100(1):135–46.
3. Zeyen TG, Caprioli J. Progression of disc and field damage in early glaucoma. Arch Ophthalmol. 1993; 111(1):62–5.
4. Zangwill LM, Bowd C, Berry CC, et al. Discriminating between normal and glaucomatous eyes using the Heidelberg retina tomograph, GDx Nerve Fiber Analyzer, and optical coherence tomograph. Arch Ophthalmol. 2001;119(7):985–93.
5. Greaney MJ, Hoffman DC, Garway-Heath DF, Nakla M, Coleman AL, Caprioli J. Comparison of optic nerve imaging methods to distinguish normal eyes from those with glaucoma. Invest Ophthalmol Vis Sci. 2002;43(1):140–5.
6. Coops A, Henson DB, Kwartz AJ, Artes PH. Automated analysis of Heidelberg retina tomograph optic disc images by glaucoma probability score. Invest Ophthalmol Vis Sci. 2006;47(12):5348–55.

7. Reus NJ, de Graaf M, Lemij HG. Accuracy of GDx VCC, HRT I, and clinical assessment of stereoscopic optic nerve head photographs for diagnosing glaucoma. Br J Ophthalmol. 2007;91(3):313–8.
8. Strouthidis NG, Garway-Heath DF. New developments in Heidelberg retina tomograph for glaucoma. Curr Opin Ophthalmol. 2008;19(2):141–8.
9. Lemij HG, Reus NJ. New developments in scanning laser polarimetry for glaucoma. Curr Opin Ophthalmol. 2008;19(2):136–40.
10. Kostanyan T, Wollstein G, Schuman JS. New developments in optical coherence tomography. Curr Opin Ophthalmol. 2015;26(2):110–5.
11. Deleon-Ortega JE, Arthur SN, McGwin Jr G, Xie A, Monheit BE, Girkin CA. Discrimination between glaucomatous and nonglaucomatous eyes using quantitative imaging devices and subjective optic nerve head assessment. Invest Ophthalmol Vis Sci. 2006;47(8):3374–80.
12. Zangwill LM, Jain S, Racette L, et al. The effect of disc size and severity of disease on the diagnostic accuracy of the Heidelberg retina tomograph glaucoma probability score. Invest Ophthalmol Vis Sci. 2007;48(6):2653–60.
13. Harizman N, Zelefsky JR, Ilitchev E, Tello C, Ritch R, Liebmann JM. Detection of glaucoma using operator-dependent versus operator-independent classification in the Heidelberg retinal tomograph-III. Br J Ophthalmol. 2006;90(11):1390–2.
14. Ferreras A, Pablo LE, Larrosa JM, Polo V, Pajarin AB, Honrubia FM. Discriminating between normal and glaucoma-damaged eyes with the Heidelberg Retina Tomograph 3. Ophthalmology. 2008;115(5):775–81 e772.
15. He L, Ren R, Yang H, et al. Anatomic vs. acquired image frame discordance in spectral domain optical coherence tomography minimum rim measurements. PLoS One. 2014;9(3):e92225.
16. Gardiner SK, Ren R, Yang H, Fortune B, Burgoyne CF, Demirel S. A method to estimate the amount of neuroretinal rim tissue in glaucoma: comparison with current methods for measuring rim area. Am J Ophthalmol. 2014;157(3):540–9.e541–2.
17. Chauhan BC, Burgoyne CF. From clinical examination of the optic disc to clinical assessment of the optic nerve head: a paradigm change. Am J Ophthalmol. 2013;156(2):218–27 e212.
18. Vizzeri G, Weinreb RN, Martinez de la Casa JM, et al. Clinicians agreement in establishing glaucomatous progression using the Heidelberg retina tomograph. Ophthalmology. 2009;116(1):14–24.
19. O'Leary N, Crabb DP, Mansberger SL, et al. Glaucomatous progression in series of stereoscopic photographs and Heidelberg retina tomograph images. Arch Ophthalmol. 2010;128(5):560–8.
20. Strouthidis NG, White ET, Owen VM, Ho TA, Hammond CJ, Garway-Heath DF. Factors affecting the test-retest variability of Heidelberg retina tomograph and Heidelberg retina tomograph II measurements. Br J Ophthalmol. 2005;89(11):1427–32.
21. Poli A, Strouthidis NG, Ho TA, Garway-Heath DF. Analysis of HRT images: comparison of reference planes. Invest Ophthalmol Vis Sci. 2008;49(9):3970–5.
22. Schuman JS, Hee MR, Puliafito CA, et al. Quantification of nerve fiber layer thickness in normal and glaucomatous eyes using optical coherence tomography. Arch Ophthalmol. 1995;113(5):586–96.
23. Drexler W, Fujimoto JG. State-of-the-art retinal optical coherence tomography. Prog Retin Eye Res. 2008;27(1):45–88.
24. Sung KR, Sun JH, Na JH, Lee JY, Lee Y. Progression detection capability of macular thickness in advanced glaucomatous eyes. Ophthalmology. 2012;119(2):308–13.
25. Vizzeri G, Weinreb RN, Gonzalez-Garcia AO, et al. Agreement between spectral-domain and time-domain OCT for measuring RNFL thickness. Br J Ophthalmol. 2009;93(6):775–81.
26. Kim JS, Ishikawa H, Gabriele ML, et al. Retinal nerve fiber layer thickness measurement comparability between time domain optical coherence tomography (OCT) and spectral domain OCT. Invest Ophthalmol Vis Sci. 2010;51(2):896–902.
27. Chen CL, Ishikawa H, Ling Y, et al. Signal normalization reduces systematic measurement differences between spectral-domain optical coherence tomography devices. Invest Ophthalmol Vis Sci. 2013;54(12):7317–22.
28. Leite MT, Rao HL, Zangwill LM, Weinreb RN, Medeiros FA. Comparison of the diagnostic accuracies of the Spectralis, Cirrus, and RTVue optical coherence tomography devices in glaucoma. Ophthalmology. 2011;118(7):1334–9.
29. Lisboa R, Paranhos A, Weinreb RN, Zangwill LM, Leite MT, Medeiros FA. Comparison of different spectral domain OCT scanning protocols for diagnosing preperimetric glaucoma. Invest Ophthalmol Vis Sci. 2013;54(5):3417–25.
30. Mwanza JC, Budenz DL, Godfrey DG, et al. Diagnostic performance of optical coherence tomography ganglion cell—inner plexiform layer thickness measurements in early glaucoma. Ophthalmology. 2014;121(4):849–54.
31. Mwanza JC, Oakley JD, Budenz DL, Anderson DR, Cirrus Optical Coherence Tomography Normative Database Study G. Ability of cirrus HD-OCT optic nerve head parameters to discriminate normal from glaucomatous eyes. Ophthalmology. 2011;118(2):241–8 e241.
32. Chauhan BC, O'Leary N, Almobarak FA, et al. Enhanced detection of open-angle glaucoma with an anatomically accurate optical coherence tomography-derived neuroretinal rim parameter. Ophthalmology. 2013;120(3):535–43.
33. Hwang YH, Kim YY. Glaucoma diagnostic ability of quadrant and clock-hour neuroretinal rim assessment using cirrus HD optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(4):2226–34.

34. Nilforushan N, Nassiri N, Moghimi S, et al. Structure-function relationships between spectral-domain OCT and standard achromatic perimetry. Invest Ophthalmol Vis Sci. 2012;53(6):2740–8.
35. Medeiros FA, Zangwill LM, Bowd C, Mansouri K, Weinreb RN. The structure and function relationship in glaucoma: implications for detection of progression and measurement of rates of change. Invest Ophthalmol Vis Sci. 2012;53(11):6939–46.
36. Pinto LM, Costa EF, Melo Jr LA, et al. Structure-function correlations in glaucoma using matrix and standard automated perimetry versus time-domain and spectral-domain OCT devices. Invest Ophthalmol Vis Sci. 2014;55(5):3074–80.
37. Danthurebandara VM, Sharpe GP, Hutchison DM, et al. Enhanced structure-function relationship in glaucoma with an anatomically and geometrically accurate neuroretinal rim measurement. Invest Ophthalmol Vis Sci. 2015;56(1):98–105.
38. Garas A, Vargha P, Hollo G. Reproducibility of retinal nerve fiber layer and macular thickness measurement with the RTVue-100 optical coherence tomograph. Ophthalmology. 2010;117(4):738–46.
39. Mwanza JC, Chang RT, Budenz DL, et al. Reproducibility of peripapillary retinal nerve fiber layer thickness and optic nerve head parameters measured with cirrusTM HD-OCT in glaucomatous eyes. Invest Ophthalmol Vis Sci. 2010;51(11):5724–30.
40. Matlach J, Wagner M, Malzahn U, Göbel W. Repeatability of peripapillary retinal nerve fiber layer and inner retinal thickness among two spectral domain optical coherence tomography devices. Invest Ophthalmol Vis Sci. 2014;55(10):6536–46.
41. Francoz M, Fenolland JR, Giraud JM, et al. Reproducibility of macular ganglion cell-inner plexiform layer thickness measurement with cirrus HD-OCT in normal, hypertensive and glaucomatous eyes. Br J Ophthalmol. 2014;98(3):322–8.
42. Kim KE, Yoo BW, Jeoung JW, Park KH. Long-term reproducibility of macular ganglion cell analysis in clinically stable glaucoma patients. Invest Ophthalmol Vis Sci. 2015.
43. Weinreb RN. Evaluating the retinal nerve fiber layer in glaucoma with scanning laser polarimetry. Arch Ophthalmol. 1999;117(10):1403–6.
44. Medeiros FA, Bowd C, Zangwill LM, Patel C, Weinreb RN. Detection of glaucoma using scanning laser polarimetry with enhanced corneal compensation. Invest Ophthalmol Vis Sci. 2007;48(7):3146–53.
45. Mai TA, Reus NJ, Lemij HG. Structure-function relationship is stronger with enhanced corneal compensation than with variable corneal compensation in scanning laser polarimetry. Invest Ophthalmol Vis Sci. 2007;48(4):1651–8.
46. Bowd C, Tavares IM, Medeiros FA, Zangwill LM, Sample PA, Weinreb RN. Retinal nerve fiber layer thickness and visual sensitivity using scanning laser polarimetry with variable and enhanced corneal compensation. Ophthalmology. 2007;114(7):1259–65.
47. Nouri-Mahdavi K, Nowroozizadeh S, Nassiri N, et al. Macular ganglion cell/inner plexiform layer measurements by spectral domain optical coherence tomography for detection of early glaucoma and comparison to retinal nerve fiber layer measurements. Am J Ophthalmol. 2013;156(6):1297–307.e1292.
48. Hood DC, Kardon RH. A framework for comparing structural and functional measures of glaucomatous damage. Prog Retin Eye Res. 2007;26(6):688–710.
49. Na JH, Sung KR, Baek S, et al. Detection of glaucoma progression by assessment of segmented macular thickness data obtained using spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(7):3817–26.

Optic Nerve: Atypical Nerves and Nerve Findings

7

Beth Edmunds and John C. Morrison

Core Messages

- Peripapillary atrophy is worth noting in the context of a possible diagnosis of glaucoma.
- There are examination tools that help to distinguish a normal tilted disc from a glaucomatous disc.
- There are examination tools that help to distinguish optic nerve head drusen from glaucoma.
- There are clinical tools that can help distinguish glaucoma from other optic nerve pathologies that may benefit from neuro-ophthalmic consultation.
- In some cases, it can be very difficult to differentiate glaucoma from other atypical nerve findings.

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7.1 Should Peripapillary Atrophy Concern Me? Should It Be Followed for Enlargement?

It is now well recognized that structural changes in the head of the optic nerve often precede functional changes detected by perimetry. The evaluation of the optic disc has therefore become increasingly important in the diagnosis and management of glaucoma, with an emphasis on early detection of the disease. As it contains the neural fibers of the optic nerve, the appearance, contour and substance of the neural rim, and inversely the extent of the optic cup, generally hold the examiner's primary attention. However, other manifestations of glaucomatous optic neuropathy may also be useful in the detection and monitoring of glaucoma. These include PPA.

Peripapillary atrophy (PPA) refers to a white or pigmented crescent-shaped area adjacent to the head of the optic nerve. As its name suggests, it represents atrophy of preexisting tissue, here the chorioretinal tissue overlying the peripapillary sclera, which is considered by many to be secondary to the glaucomatous process. The atrophy may be confined to a small area adjacent to the disc, often temporal, or inferior and temporal. It may also be extensive and surround the disc concentrically for some distance. In glaucoma patients, its extent may be correlated with the amount of nerve rim loss and field loss [1].

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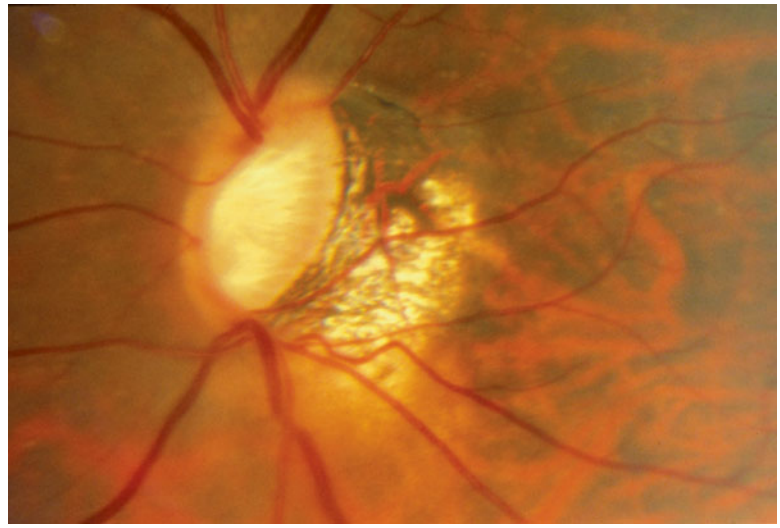

Fig. 7.1 Peripapillary atrophy in myopic tilted disc with glaucoma

Jonas has divided the area of PPA into two zones based on the extent of tissue atrophy [2]. Zone α is thought to represent pigmentary and structural irregularity of retinal pigment epithelial cells (RPE), and is clinically recognized as a crescent or halo of irregular hypo/hyper pigmentation which may separate the disc from the β zone, or be adjacent to the optic disc in the absence of a β zone [3]. In the β zone, there is complete loss of the RPE cells accompanied by variable loss of the photoreceptors, appearing as visible bared sclera and large choroidal vessels [3]. If large enough, either type of PPA can contribute to an enlarged blind spot on perimetry [4].

PPA, in particular of zone β, is found more frequently in glaucoma patients than in the general population, but not exclusively so. Its extent generally correlates with the degree of optic nerve damage and field loss. However, in a recent study ranking various optic nerve parameters for their sensitivity and specificity in detecting early glaucomatous change, PPA was one of the least discriminatory variables [5]. While it should be used to guide the clinician to examine the corresponding area of the disc more closely in suspected early glaucomatous optic neuropathy [6], it is currently neither sensitive nor specific enough to use by itself for routine early detection of glaucoma.

Detecting disease progression in patients with established glaucomatous optic neuropathy requires sequential comparison of optic disc morphology and the nerve fiber layer over a period of time. A large zone β at baseline [7] or increasing zone β atrophy over a period of time [8] have been associated with progressive glaucomatous optic neuropathy and field defects. Several imaging modalities have been developed to quantify parameters that characterize glaucoma to allow sequential comparison but further studies are required to assess the value of including PPA as such a parameter.

One of the weaknesses of using the presence of PPA to establish a glaucoma diagnosis is that deficiencies of the peripapillary chorioretinal tissue can also be found in other conditions. The temporal crescent found in pathological myopia is histologically different than zone β atrophy; however, clinically it can appear similar. As in glaucoma, this area can increase in size and extent due to progressive stretching of the globe and temporal shifting and atrophy of the peripapillary margins of the chorioretinal layers [9]. However, as myopia is itself a risk factor for glaucoma [10–12] it may be difficult to interpret the significance of PPA or its progression in these eyes (Fig. 7.1). Secondary PPA can also be found in ocular histoplasmosis, Vogt-Koyanagi-Harada and other uveitides, and as a part of normal aging [13]. The scleral, RPE, and choroidal crescents and haloes seen in tilted discs and colobomas may also give the appearance of PPA. However,

these are primary in origin rather than a secondary atrophy, and are not expected to progress. Optic neuropathies other than glaucomatous optic neuropathy do not generally lead to the development of PPA although PPA and temporal cupping have been reported in autosomal dominant optic atrophy [14].

Summary for the Clinician

- PPA is associated with glaucoma but is not a particularly sensitive or specific parameter for early diagnosis.
- PPA is a predictor of and associated with glaucoma progression.
- Zone β PPA can be associated with glaucoma and glaucomatous disc progression.
- PPA or PPA-like findings can occur in other diseases or can be a normal variant.
- PPA is worth noting but currently is difficult to quantify or monitor reliably.
- PPA is not yet a "stand alone" tool for the management of glaucoma, but its presence should alert the practitioner to scrutinize carefully the appearance and substance of the neural rim and nerve fiber layer, particularly in the region corresponding to the location of the PPA.

7.2 In Examining Tilted Optic Discs, How Do I Distinguish Tilt vs. Glaucoma?

7.2.1 What Are the Characteristics of a Tilted Disc?

The tilted disc is produced by an oblique insertion of the optic nerve into the globe, which produces relative prominence of the anterior pole and the impression of tilting about an axis. Its contour appears more oval and tilted when viewed, with increasing obliquity. The relative prominence of one pole and gradual recessed slope of the other can give the appearance of rim thinning in the latter and raise the suspicion of glaucoma. Tilted discs can occur as part of the congenital tilted disc (CTD) syndrome, be related to myopia (myopic tilted disc, MTD) or present as isolated phenomena. Many studies of tilted discs do not distinguish among these entities.

Tilting can occur in any direction; in the CTD syndrome, it is generally inferonasal [9, 15] while in myopia it is usually temporal in orientation [9, 16]. Either can cause the disc to appear glaucomatous. Other features accompanying the obliquity of nerve insertion are a scleral crescent, PPA, oblique entry of vessels following the orientation of the tilted disc (sometimes called situs inversus in cases of nasal tilting), posterior staphyloma, and chorioretinal thinning [9, 15, 17] (Fig. 7.2). Similar crescents and PPA can be seen adjacent to the affected sectors of a glaucomatous optic nerve, which adds further to the difficulty of distinguishing between the two [9].

Both CTD and MTD are associated with myopia and astigmatism [9, 18–20] with the degree of the tilt of the disc correlated with severity of ametropia [19, 21]. Myopia itself is a risk factor for glaucoma [10–12] bringing a two- to threefold increased risk when controlled for all other risk factors including intraocular pressure (IOP) [11]. Tilted discs therefore not only masquerade as glaucoma, but also are more at a risk of developing glaucoma than un-tilted discs.

7.2.2 Can My Patient Help Me to Distinguish Between Tilt and Glaucoma?

Early glaucoma and tilted discs are both usually detected in asymptomatic patients, who generally have normal central acuities and asymptomatic field defects. However, a recent study showed color vision aberrations in up to 50 % of CTD subjects, regardless of the extent of visual field disturbance or visual acuity [22]. This would not be expected in glaucomatous optic neuropathy with similar degrees of VF loss. Family history can also help determine the significance of equivocal discs. A family history of glaucoma would influence the probability

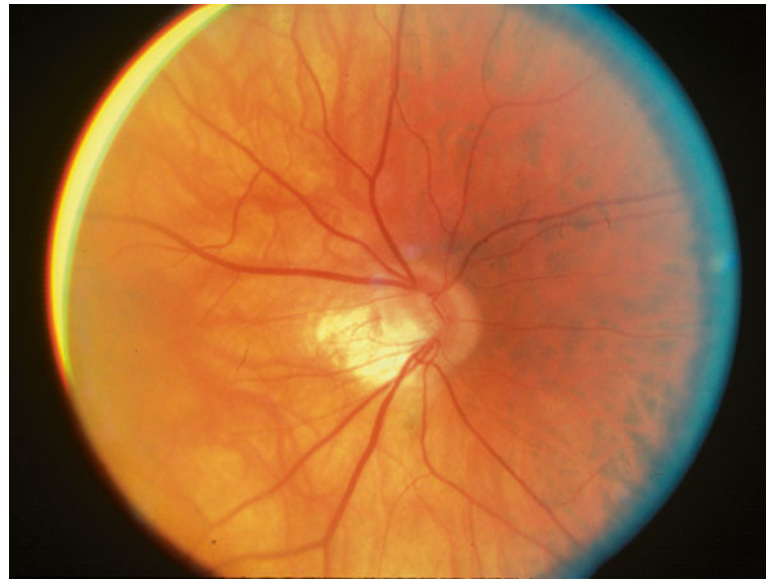

Fig. 7.2 Congenital tilted disc showing scleral crescent and situs inversus

towards this diagnosis, while Asian ancestry may favor tilted disc, due to higher rates of myopia and MTDs in these populations than in Caucasians [16, 23]. Other risk factors for glaucoma such as nerve fiber layer hemorrhages and high IOP would also increase the suspicion of glaucoma.

7.2.3 Can Perimetry Help Me to Distinguish Between Tilt and Glaucoma?

Tilted discs may be accompanied by a variety of field defects that usually correspond to the direction of the tilt [15] and are most frequently described superiorly [15] or in the superotemporal quadrant [19, 24, 25]. In the CTD syndrome, the field defects have been ascribed to the anomalous development of the inferonasal aspect of the optic nerve and retina [9, 15] and are considered stable [9]. They tend to be relative scotomas and, like glaucoma, do not respect the vertical midline [9], which should help rule out a temporal or bitemporal hemianopsia. A more recent study of visual field defects in MTDs in young Chinese men who were carefully refracted and had no risk factors for glaucoma failed to find any field defects [21]. This might imply that progressive field loss must occur in MTDs to explain the associated defects found in older people. This makes the distinction from glaucoma, on the basis of perimetric progression, more difficult.

Quantification of the field defect produced by tilting in these patients is confounded by the potential contributions of refractive error and coexisting pathology. Many of the original studies describing tilted discs may have inadvertently included glaucomatous eyes as well as other pathologies not recognized to interfere with perimetry. Myopia itself reduces mean retinal sensitivity and associated astigmatism can also influence perimetric performance. Guiffre suggested that, in some cases, refractive scotomas could result from the difference in height between the normal and relatively ectatic retinal sectors [17]. A recent study of Goldman perimetry in subjects with tilted discs showed that careful correction of refractive error reduced or eliminated the visual field defect in 50 % of cases [24]. In another, where perimetry was performed using contact lenses and/or trial frame correction, no visual field defects were detected, despite myopic disc tilting [21].

Therefore, it is important to pay meticulous attention to the patient's refraction when attempting to detect field defects and monitor progression in these patients. Carefully correlating the disc

appearance with the field defect may also help the clinician distinguish between tilted discs (which should be stationary) and glaucoma (which could progress). However, this can still be very difficult, particularly in an eye with a tilted disc and a glaucomatous-looking superotemporal arcuate scotoma that crosses the vertical meridian. Furthermore, both glaucomatous optic neuropathy and MTDs can show progressive field loss. It must also be emphasized that, even though CDT is considered stationary, these eyes are clearly at higher risk of developing glaucoma and thus may also develop progressive field loss.

7.2.4 Can Optic Nerve Imaging Help Me to Distinguish Between Tilt and Glaucoma?

All of the calculated parameters in the HRT analysis are dependent on the position of a reference plane. This plane is automatically set perpendicular to the *z* axis and based on a normative database. As a tilted disc may not have a normal relationship between the surface of the optic nerve head and the reference plane this can lead to sectoral errors in measurement of many of the cup and retinal nerve fiber layer (RNFL) parameters [20, 26, 27]. In a study of healthy Chinese Singaporean children specifically controlled for refractive error (myopia), all HRT disc parameters (except maximum cup depth) and NFL measurements were strongly influenced by the tilting of the head of the optic nerve [20]. Theoretically, PPA or staphylomatous changes that may accompany tilted discs may also interfere with the HRT analysis. Strategies to improve the ability of the HRT to detect glaucoma in tilted discs have been proposed, such as adjusting the height of the reference plane according to the mean peripapillary NFL thickness calculated by OCT [26], but these still need further evaluation.

In a study comparing GDx-VCC (GDx-variable corneal compensator) and OCT measurements of RNFL thickness in glaucomatous eyes without tilted discs [28], both techniques detected stage-dependent differences in NFL thickness with increasing severity of field defect. However in glaucomatous eyes *with* tilted discs, there was a marked discrepancy in performance. The GDx-VCC generated higher values of NFL thickness than OCT and also failed to correlate NFL thickness with the severity of the glaucomatous field defect. In contrast, OCT-generated NFL thickness correlated well with mean pattern deviation in each hemi field and with overall mean deviation in both the tilted and un-tilted groups. At this stage, OCT therefore seems the most useful of the imaging modalities for detecting and following glaucoma in eyes with tilted discs.

7.2.5 What Management Strategy Can I Use in Equivocal Cases of Tilt vs. Glaucoma?

Although one does not want to treat patients for glaucoma unnecessarily [29], the presence of a tilted disc raises the differential diagnosis of glaucoma as well as the possibility of superimposed glaucoma. We recommend that if the diagnosis is equivocal, but there are other risk factors for glaucoma such as high IOP or a positive family history, treatment should be considered. Likewise, if progression can be demonstrated, either as increased cupping or deteriorating field, the patient should be treated for glaucoma.

Summary for Clinicians

- Tilting of the optic disc can occur as an isolated phenomenon or as part of the myopic or congenitally tilted disc spectrum.
- The tilted disc may appear glaucomatous and also present with glaucomatous-like field defects.
- Patients with tilted discs and myopia are at higher risk of developing glaucoma.
- Meticulous correction of spherical and astigmatic refractive errors should be used when examining the VF in eyes with tilted discs.
- Abnormal color vision is more likely in congenitally tilted discs than glaucomatous

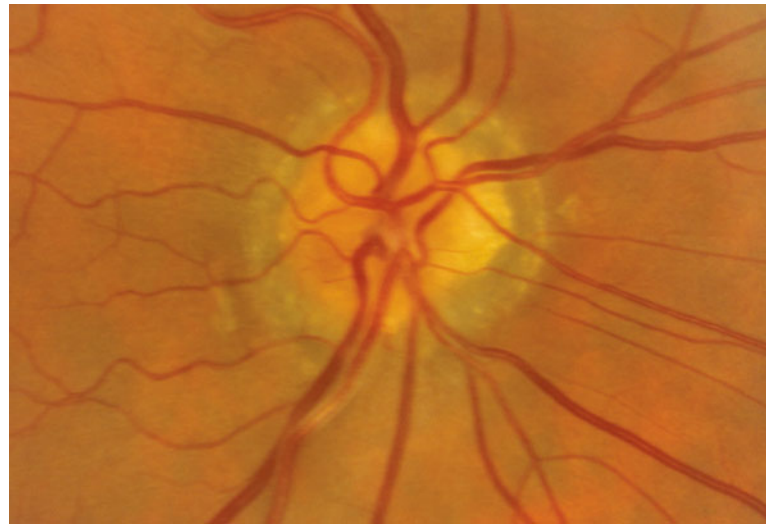

Fig. 7.3 Exposed optic nerve head drusen in small optic nerve

optic neuropathy for similar degrees of VF involvement.

- VF defects are progressive in glaucoma and myopic tilted discs but stationary in congenitally tilted discs unless there is other pathology.
- Heidelberg retinal tomography (HRT) and GDx do not perform well in tilted discs, nerve fiber layer measurement by ocular coherence tomography (OCT) is currently the best modality for structural imaging.
- The clinician should have a low threshold for treating patients with tilted discs who have other risk factors for glaucoma.

7.3 With Optic Nerve Head Drusen, How Do I Tell If Visual Field Changes Are Due to Drusen vs. Glaucoma?

7.3.1 Description of Drusen

Optic nerve head drusen (OND) are prelaminar collections of extracellular mucopolysaccharides, proteins, iron, and calcium [30, 31] that slowly increase in size with progressive calcium deposition and cause axonal compression within the scleral canal [32]. Their reported prevalence varies between 3.4 and 20.4 per 1000, and they are frequently bilateral [33]. They usually occur in eyes with small optic nerve canals [34, 35], which has been thought to contribute both to their development [34, 36] and their effect on the visual field [35], though this has recently been questioned [37]. OND are usually buried within the nerve head in early life but become more visible with age [38], which may in part explain their reported increased frequency in older people. When buried, the nerve head may appear full without a cup and the overlying vasculature may show abnormal branching patterns and capillarity [39]. A small disc and retinal vasculature emanating from its center are also clues to the presence of buried drusen. Once exposed, they are lumpy, sometimes refractile, autofluorescent bodies in the nerve head (Fig. 7.3). OND are often isolated anomalies but can be complicated by ischemic events such as anterior ischemic optic neuropathy, isolated hemorrhage, or hemorrhage from associated sub-retinal revascularization which can cause sudden loss of acuity. They may also be associated with retinitis pigmentosa, angioid streaks, and other rare disorders [33]. Their effect on the appearance of the optic disc can also lead to the misdiagnosis of papilledema.

7.3.2 What Are the Characteristics of Field Defects in OND?

Depending on study criteria, a variable proportion of eyes with OND will have visual field disturbances [35, 40–44], which may or may not be symptomatic. In a retrospective study, possibly affected by recall bias, 50 % of patients with visual field defects due to OND were aware of visual disturbance, even though the majority had acuities of 20/20 [43]. Some of the reported field defects are atypical of glaucoma, such as an enlarged blind spot, sudden altitudinal loss and central defects that may be accompanied by a drop in acuity due to the complications mentioned above. However, those drusen presenting with arcuate defects or generalized reduction in sensitivity can simulate glaucomatous visual field loss. The focal field defects are thought to be caused by nerve fiber damage, due to the interruption of circulatory or axoplasmic flow in the nerve head by the physical crowding the drusen impose in the scleral canal [40, 44, 45]. A recent automated visual field study of subjects with buried OND, and with normal ophthalmic examinations, found NFL-type defects in 5 % of subjects [42]. Likewise in children, whose drusen are usually buried, visual field defects are less commonly found than in adults. However, with increasing age, and exposure of the drusen, field defects become more frequent [41, 43, 45] and more severe [46, 47].

The focal field defects are frequently bilateral and usually occupy the inferior sector of the field as inferior or inferonasal arcuate scotomas [40, 42–44]. When presenting like this, it is very difficult to distinguish them from glaucomatous arcuate scotomas. Progression is slow [46, 47] and has been reported in 0–40 % [46] of cases. This can particularly resemble normal tension glaucoma, in which a sizable proportion of cases are also considered nonprogressive. In both conditions, it is impossible to predict who these patients will be.

7.3.3 Are There Other Signs That Can Help Me Distinguish Between OND and Glaucoma?

In unilateral or highly asymmetric drusen a relative afferent pupillary defect can be found on the side with the more profound visual field loss [43], whereas in glaucoma a relative afferent pupillary defect is not usually present unless there is a more severe disparity in disease between the two eyes. Fundoscopy in coexisting OND and early glaucoma may not help discriminate between these two potential causes of arcuate field defect as the drusen may obscure early glaucomatous nerve head changes. However, as glaucomatous optic neuropathy progresses, concomitant with increasing age, the drusen become more exposed, and glaucomatous damage of the neuroretinal rim is easier to understand. Where drusen cause an enlarged blind spot, an altitudinal defect, or central acuity loss, it is easier to ascribe the perimetric findings to OND, although glaucoma with PPA can also produce arcuate defects accompanied by an enlarged blind spot. Examination of the disc should help make this distinction. Unlike glaucoma, the apparent position of the drusen within the disc does not necessarily correlate with the location of the field defects [40, 44].

7.3.4 Can Imaging Help Me to Distinguish Between OND and Glaucoma?

OND are associated with nerve fiber layer thickness defects that can be generalized or focal, most often in the nasal peripapillary area. Both OCT and scanning laser ophthalmoscopy (SLO) have been used to study RNFL thickness in OND. Optical coherence tomography (OCT) showed greater sensitivity than red free photography in detecting NFL thinning in some eyes with OND, correlating greater NFL thinning with increasing grade of drusen and visual field defect [48]. Two studies of SLO show a correlation between NFL thinning and visual field defects but conflicting evidence of a relationship between visibility of the drusen and NFL thinning [49, 50]. These NFL defects are indistinguishable from those caused by glaucoma. Serial NFL imaging may be helpful to document progression, but cannot help in distinguishing between progression caused by glaucoma vs. OND.

B-scan ultrasonography is the gold-standard tool for detecting OND and is superior to fluorescein angiography, computed tomography, or SLO

scanning [51]. B-scan is therefore useful where there is suspicion of undiagnosed drusen causing a visual field defect. It is also useful in distinguishing drusen from papilledema or other causes of optic disc swelling.

7.3.5 What Management Strategy Can I Use in Equivocal Cases of OND vs. Glaucoma?

When deciding whether or not to treat a patient with OND, one needs to take other factors into consideration. In the patient with elevated IOP (or a normotensive patient with thin corneas), patient with a family history of glaucoma, or where there is any suggestion of glaucomatous disc change around the drusen, IOP lowering is indicated. An argument can also be made to lower the pressure in any patient where this can be achieved without significant side effects, regardless of the suspicion of glaucoma. This could protect the nerve from ischemic events as well as potentially protect nerve fibers with threatened axoplasmic flow from crowding of the nerve fibers within the nerve head.

Although Occam's razor is usually appropriate, there should always be skepticism about any field change that does not correlate with disc findings and neurological imaging should be considered to exclude compressive lesions of the optic nerve [52].

Summary for the Clinician

- OND generally occur in small optic nerve canals and can cause arcuate scotomas indistinguishable from glaucoma.
- The presence of drusen may obscure visualization of disc tissue and glaucomatous change.
- Apart from the predilection of OND to cause inferior sector field defects, it is impossible to distinguish between the arcuate field defects produced by glaucoma and drusen based on their perimetric appearance.
- Arcuate visual field defects associated with symptoms of reduced acuity are more likely to be caused by drusen than glaucoma.
- Arcuate visual field defects from unilateral OND are more likely to be accompanied by a relative afferent pupillary defect than similar field asymmetry in unilateral glaucoma.
- B-scan ultrasonography may identify buried drusen and explain an arcuate defect in a patient whose optic nerve does not have any corresponding signs of glaucoma.
- Be aware that, as with glaucoma, visual fields that do not correlate with the disc appearance may be indicative of other pathology, even if drusen are present.
- Dense or extensive field defects in cases with buried drusen should prompt a search for other causes of field loss.
- Have a low threshold for lowering IOP in OND—check CCT, inquire about a family history of glaucoma and monitor IOP and visual fields in all patients with OND.
- Even though the mechanism of axonal damage is probably different in OND, lowering IOP may help protect axonal function.
- The clinician should have a low threshold for treating patients with OND and risk factors for glaucoma, and consider lowering IOP even in the absence of glaucoma in some cases.

7.4 What Differential Diagnosis Should Be Kept in Mind When Looking at a Case of Questionable Glaucoma?

7.4.1 What is the Significance of Disc Cupping?

The most discriminatory feature separating glaucomatous optic neuropathy from other optic atrophies is the presence of pathological cupping.

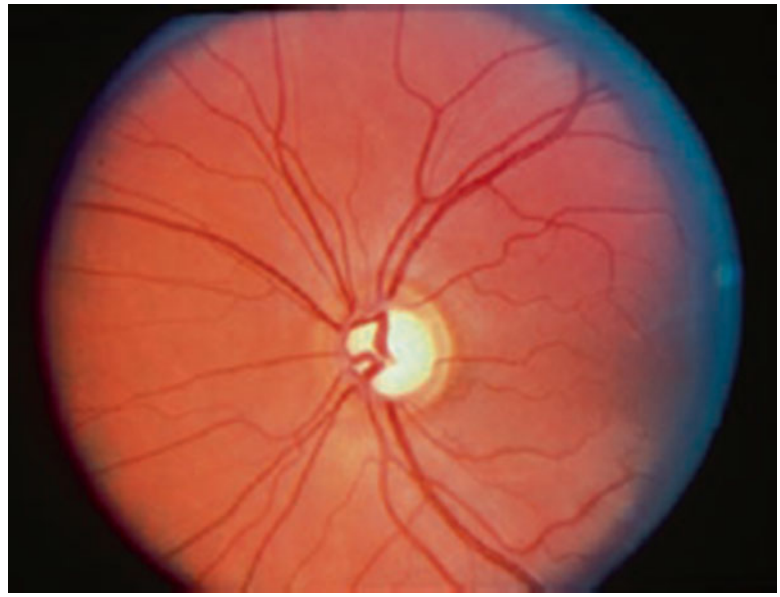

Fig. 7.4 Large physiological cup in large optic disc

This is caused by loss of tissue in the neuroretinal rim, which can be focal and/or diffuse. Focal neuroretinal rim loss is usually first detected in the superior and inferior poles of the nerve and results in vertical elongation of the physiological cup and ultimately notching and undermining. Diffuse neuroretinal rim loss is more concentric in appearance with generalized rim thinning and excavation of the cup. The accompanying perimetric changes reflect this disc pathology: focal field defects correspond to focal damage of nerve fiber bundles in the optic nerve head, and generalized reduction of sensitivity reflects diffuse neuroretinal rim loss. Other features of glaucomatous cupping have been discussed in detail in Chap. 2.

The vertical cup-to-disc ratio (VCDR) is a useful clinical measure for quantifying the degree of disc cupping and can be performed easily at the slit lamp. A VCDR greater than the 97.5th percentile, which is approximately 0.7 for most populations [53], is now a recommended diagnostic criterion for glaucoma studies [54]. However, although the risk of development or progression of glaucoma is strongly associated with increasing cup size [7, 55–57], this absolute cutoff can be a blunt instrument when dealing with the individual patient. It is well recognized that large discs may be accompanied by large cups, which are physiological rather than pathological [58] and this results in the diagnostic dilemma of distinguishing between the two (Fig. 7.4).

7.4.2 How Do I Tell the Difference Between Physiological Large Cupping and Glaucomatous Cupping?

Careful disc examination is required to detect subtle early glaucomatous changes in the NFL or disc. Ideally, this should be performed after pupillary dilation as a binocular stereoscopic view is helpful when assessing many of these features. Several studies have also shown how, even in the hands of experts, CDR is underestimated by monocular examination [59–61]. In the presence of the other hallmarks of glaucomatous optic neuropathy (notching, NFL hemorrhage, vessel baring, PPA, etc.) and corresponding visual field defects, distinction between glaucomatous and physiological cupping is not difficult, especially in the setting of raised IOP. However, in the concentrically enlarged cup with no focal glaucomatous features, a normal field and no risk factors for glaucoma, there is a diagnostic dilemma. A larger overall disc size may be

comforting to the clinician, but still does not entirely exclude the diagnosis as patients with physiological cupping are not immune from glaucoma. Correcting VCDR for vertical disc diameter may provide a more sensitive and specific measure of glaucomatous risk [5, 62, 63] and is easily performed at the slit lamp [64]. Racial background contributes to disc size, as Caucasians have smaller discs and Black Americans have larger more vertically oval discs with larger VCDRs [64, 65]. However, the latter group also has a higher prevalence of glaucoma [66, 67]. Imaging studies may or may not be helpful; many rely on comparison between the patient and a normative database, which may not include normals with extreme disc sizes [68, 69]. Ultimately, the final arbitrator is time: a physiologically cupped disc will not increase in size or result in field defects, a pathologically cupped disc is more likely to do both. This may be the greatest strength of imaging techniques, due to their objectivity and ability to store measurements for later comparison.

7.4.3 What Is the Significance of Optic Disc Pallor?

The "pallor" seen in glaucomatous optic neuropathy refers to the color in the base of the cup, which is produced by the loss of neural, supporting and vascular tissue, and exposure of the white lamina. The "pallor" should not extend beyond the base of the cup and the remaining neural rim retains its normal yellow-pink color. Many of the optic atrophies, whether inherited, compressive, toxic, traumatic, or ischemic in etiology, have been listed in the differential diagnosis of glaucoma [70], but cupping in these cases is infrequent and appears atypical of glaucoma, and the neuroretinal rim itself is pale. In a study of optic disc photographs examined by experienced ophthalmologists masked to the underlying diagnosis, focal or diffuse obliteration of the rim was 87 % specific in predicting glaucomatous cupping, though rim thinning was only 47 % specific for glaucoma. Rim pallor was 94 % specific in predicting nonglaucomatous cupping [71], though it may not be particularly sensitive [72]. Although many of these conditions can also cause loss of the RNFL, few of them produce PPA, which can also help make the distinction [64].

7.4.4 When Do I Request Neuro-Imaging or Help from My Neuro-Ophthalmology Colleague?

Signs that should alert the clinician to a nonglaucomatous, or coexisting cause of optic disc cupping are those younger than 50 years, reduced visual acuity, visual field defects that respect the vertical midline, and neuroretinal rim pallor [72] (Fig. 7.5). Additional signs that suggest other pathological processes are headache, symptoms of hypothalamic pituitary dysfunction, loss of color vision, and relative afferent pupillary defect. An afferent defect in glaucoma is rare unless the optic neuropathy is markedly asymmetrical and highly advanced on one side. A disparity between the degree or sector of glaucomatous cupping and the nature of the visual field defects should also arouse suspicion of an alternative etiology. Under these circumstances, the patient should also be investigated for other causes of optic neuropathy or visual field loss. Unless the practitioner is comfortable with performing a full neuro-ophthalmological evaluation and ordering appropriate investigations on this basis, he/she should request a consultation from a neuro-ophthalmologist. This ensures that neuro-imaging studies will be properly directed by the physical findings of the entire visual system.

Summary for the Clinician

- Cupping is a key feature of glaucomatous optic neuropathy but can also be found in other optic neuropathies.
- Dilated disc examination is required to provide an adequate binocular view for stereoscopic assessment of cup depth and distribution of pallor, and to facilitate slit-lamp measurement of vertical disc diameter and cup-to-disc ratio.

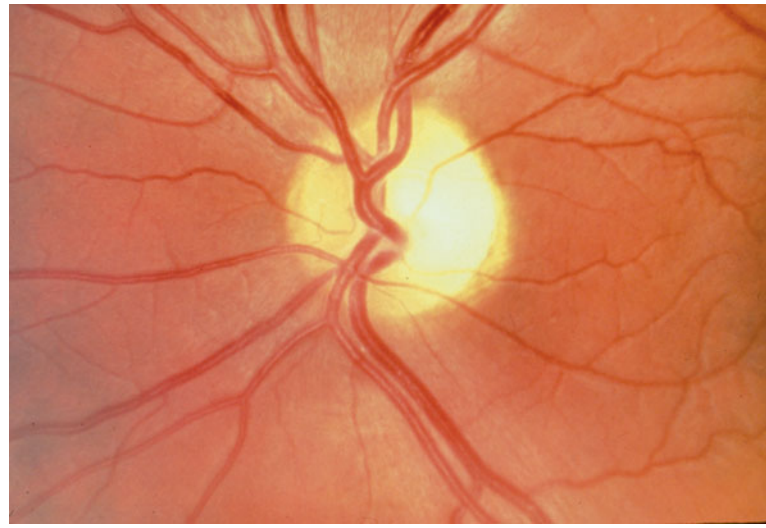

Fig. 7.5 Sectoral neuro-retinal rim pallor resulting from optic nerve compression by pituitary tumor

- Measure overall disc size (vertical disc diameter) to provide a context for the cup size—large discs may have physiologically large cups while small discs may have small cups which carry the possibility of masking changes we more classically associate with glaucomatous damage.
- Physiologically large cups may be normal in large discs, but this can only be diagnosed with certainty in retrospect, when there has been no glaucomatous change over a period of time.
- Monitoring for change over a time period may ultimately be the only way to distinguish between glaucomatous pathology vs. individual anatomy in patients with large discs.
- Although the base of the cup in glaucomatous optic neuropathy is pale, giving the impression of optic disc pallor, the remaining neuroretinal rim maintains its yellow-pink color. In the absence of other pathology, a glaucoma disc should not be described as "pale."
- Pallor of the neuroretinal rim should prompt the clinician to consider non-glaucomatous causes of the disc changes and field loss.
- If visual field loss does not correlate with glaucomatous features on disc examination, suspect another etiology and request assistance from an appropriate specialist.

References

1. Park KH, Tomita G, Liou SY, et al. Correlation between peripapillary atrophy and optic nerve damage in normal-tension glaucoma. Ophthalmology. 1996;103(11):1899–906.
2. Jonas JB, Nguyen XN, Gusek GC, et al. Parapapillary chorioretinal atrophy in normal and glaucoma eyes. I. Morphometric data. Invest Ophthalmol Vis Sci. 1989;30(5):908–18.
3. Kubota T, Jonas JB, Naumann GO. Direct clinicohistological correlation of parapapillary chorioretinal atrophy. Br J Ophthalmol. 1993;77(2):103–6.
4. Jonas JB, Gusek GC, Fernandez MC. Correlation of the blind spot size to the area of the optic disk and parapapillary atrophy. Am J Ophthalmol. 1991; 111(5):559–65.
5. Jonas JB, Bergua A, Schmitz-Valckenberg P, et al. Ranking of optic disc variables for detection of glaucomatous optic nerve damage. Invest Ophthalmol Vis Sci. 2000;41(7):1764–73.
6. Emdadi A, Kono Y, Sample PA, et al. Parapapillary atrophy in patients with focal visual field loss. Am J Ophthalmol. 1999;128(5):595–600.
7. Jonas JB, Martus P, Horn FK, et al. Predictive factors of the optic nerve head for development or

progression of glaucomatous visual field loss. Invest Ophthalmol Vis Sci. 2004;45(8):2613–8.
8. Uchida H, Ugurlu S, Caprioli J. Increasing peripapillary atrophy is associated with progressive glaucoma. Ophthalmology. 1998;105(8):1541–5.
9. Apple DJ, Rabb MF, Walsh PM. Congenital anomalies of the optic disc. Surv Ophthalmol. 1982;27(1):3–41.
10. Grodum K, Heijl A, Bengtsson B. Refractive error and glaucoma. Acta Ophthalmol Scand. 2001;79(6): 560–6.
11. Mitchell P, Hourihan F, Sandbach J, et al. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology. 1999;106(10): 2010–5.
12. Chihara E, Liu X, Dong J, et al. Severe myopia as a risk factor for progressive visual field loss in primary open-angle glaucoma. Ophthalmologica. 1997;211(2): 66–71.
13. Curcio CA, Saunders PL, Younger PW, et al. Peripapillary chorioretinal atrophy: Bruch's membrane changes and photoreceptor loss. Ophthalmology. 2000;107(2):334–43.
14. Votruba M, Thiselton D, Bhattacharya SS. Optic disc morphology of patients with OPA1 autosomal dominant optic atrophy. Br J Ophthalmol. 2003;87(1): 48–53.
15. Dorrell D. The tilted disc. Br J Ophthalmol. 1978;62(1):16–20.
16. Tong L, Saw SM, Chua WH, et al. Optic disk and retinal characteristics in myopic children. Am J Ophthalmol. 2004;138(1):160–2.
17. Giuffre G. Chorioretinal degenerative changes in the tilted disc syndrome. Int Ophthalmol. 1991;15(1):1–7.
18. Jonas JB, Kling F, Grundler AE. Optic disc shape, corneal astigmatism, and amblyopia. Ophthalmology. 1997;104(11):1934–7.
19. Vongphanit J, Mitchell P, Wang JJ. Population prevalence of tilted optic disks and the relationship of this sign to refractive error. Am J Ophthalmol. 2002; 133(5):679–85.
20. Tong L, Chan YH, Gazzard G, et al. Heidelberg retinal tomography of optic disc and nerve fiber layer in Singapore children: variations with disc tilt and refractive error. Invest Ophthalmol Vis Sci. 2007; 48(11):4939–44.
21. Tay E, Seah SK, Chan SP, et al. Optic disk ovality as an index of tilt and its relationship to myopia and perimetry. Am J Ophthalmol. 2005;139(2):247–52.
22. Vuori ML, Mantyjarvi M. Tilted disc syndrome and colour vision. Acta Ophthalmol Scand. 2007;85(6): 648–52.
23. Saw SM, Tong L, Chua WH, et al. Incidence and progression of myopia in Singaporean school children. Invest Ophthalmol Vis Sci. 2005;46(1):51–7.
24. Vuori ML, Mantyjarvi M. Tilted disc syndrome may mimic false visual field deterioration. Acta Ophthalmol Scand. 2008;86(6):622–65.
25. Brazitikos PD, Safran AB, Simona F, et al. Threshold perimetry in tilted disc syndrome. Arch Ophthalmol. 1990;108(12):1698–700.
26. Park KH, Caprioli J. Development of a novel reference plane for the Heidelberg retina tomograph with optical coherence tomography measurements. J Glaucoma. 2002;11(5):385–91.
27. Yamazaki Y, Yoshikawa K, Kunimatsu S, et al. Influence of myopic disc shape on the diagnostic precision of the Heidelberg Retina Tomograph. Jpn J Ophthalmol. 1999;43(5):392–7.
28. Yu S, Tanabe T, Hangai M, et al. Scanning laser polarimetry with variable corneal compensation and optical coherence tomography in tilted disk. Am J Ophthalmol. 2006;142(3):475–82.
29. Doshi A, Kreidl KO, Lombardi L, et al. Nonprogressive glaucomatous cupping and visual field abnormalities in young Chinese males. Ophthalmology. 2007; 114(3):472–9.
30. Boyce SW, Platia EV, Green WR. Drusen of the optic nerve head. Ann Ophthalmol. 1978;10(6):695–704.
31. Friedman AH, Beckerman B, Gold DH, et al. Drusen of the optic disc. Surv Ophthalmol. 1977;21(5):373–90.
32. Tso MO. Pathology and pathogenesis of drusen of the optic nerve head. Ophthalmology. 1981;88(10): 1066–80.
33. Auw-Haedrich C, Staubach F, Witschel H. Optic disk drusen. Surv Ophthalmol. 2002;47(6):515–32.
34. Mullie MA, Sanders MD. Scleral canal size and optic nerve head drusen. Am J Ophthalmol. 1985;99(3):3 56–9.
35. Jonas JB, Gusek GC, Guggenmoos-Holzmann I, et al. Optic nerve head drusen associated with abnormally small optic discs. Int Ophthalmol. 1987;11(2):79–82.
36. Spencer WH. Drusen of the optic disk and aberrant axoplasmic transport. The XXXIV Edward Jackson memorial lecture. Am J Ophthalmol. 1978;85(1):1–12.
37. Floyd MS, Katz BJ, Digre KB. Measurement of the scleral canal using optical coherence tomography in patients with optic nerve drusen. Am J Ophthalmol. 2005;139(4):664–9.
38. Spencer TS, Katz BJ, Weber SW, et al. Progression from anomalous optic discs to visible optic disc drusen. J Neuroophthalmol. 2004;24(4):297–8.
39. Sacks JG, O'Grady RB, Choromokos E, et al. The pathogenesis of optic nerve drusen. A hypothesis. Arch Ophthalmol. 1977;95(3):425–8.
40. Lorentzen SE. Drusen of the optic disk. A clinical and genetic study. Acta Ophthalmol (Copenh). 1966;Suppl 90:1–180.
41. Mustonen E. Pseudopapilloedema with and without verified optic disc drusen. A clinical analysis II: visual fields. Acta Ophthalmol (Copenh). 1983;61(6): 1057–66.
42. Katz BJ, Pomeranz HD. Visual field defects and retinal nerve fiber layer defects in eyes with buried optic nerve drusen. Am J Ophthalmol. 2006;141(2):248–53.
43. Wilkins JM, Pomeranz HD. Visual manifestations of visible and buried optic disc drusen. J Neuroophthalmol. 2004;24(2):125–9.
44. Savino PJ, Glaser JS, Rosenberg MA. A clinical analysis of pseudopapilledema. II. Visual field defects. Arch Ophthalmol. 1979;97(1):71–5.

45. Cohen DN. Drusen of the optic disc and the development of field defects. Arch Ophthalmol. 1971;85(2): 224–6.
46. Lansche RK, Rucker CW. Progression of defects in visual fields produced by hyaline bodies in optic disks. AMA Arch Ophthalmol. 1957;58(1):115–21.
47. Lee AG, Zimmerman MB. The rate of visual field loss in optic nerve head drusen. Am J Ophthalmol. 2005;139(6):1062–6.
48. Roh S, Noecker RJ, Schuman JS, et al. Effect of optic nerve head drusen on nerve fiber layer thickness. Ophthalmology. 1998;105(5):878–85.
49. Mistlberger A, Sitte S, Hommer A, et al. Scanning laser polarimetry (SLP) for optic nerve head drusen. Int Ophthalmol. 2001;23(4–6):233–7.
50. Tatlipinar S, Kadayifcilar S, Bozkurt B, et al. Polarimetric nerve fiber analysis in patients with visible optic nerve head drusen. J Neuroophthalmol. 2001;21(4):245–9.
51. Kurz-Levin MM, Landau K. A comparison of imaging techniques for diagnosing drusen of the optic nerve head. Arch Ophthalmol. 1999;117(8):1045–9.
52. Mustonen E, Kallanranta T, Toivakka E. Neurological findings in patients with pseudopapilloedema with and without verified optic disc drusen. Acta Neurol Scand. 1983;68(4):218–30.
53. Broman AT, Quigley HA, West SK, et al. Estimating the rate of progressive visual field damage in those with open-angle glaucoma, from cross-sectional data. Invest Ophthalmol Vis Sci. 2008;49(1):66–76.
54. Foster PJ, Buhrmann R, Quigley HA, et al. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002;86(2):238–42.
55. Araie M, Sekine M, Suzuki Y, et al. Factors contributing to the progression of visual field damage in eyes with normal-tension glaucoma. Ophthalmology. 1994;101(8):1440–4.
56. Tezel G, Siegmund KD, Trinkaus K, et al. Clinical factors associated with progression of glaucomatous optic disc damage in treated patients. Arch Ophthalmol. 2001;119(6):813–8.
57. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):714–20; discussion 829–30.
58. Jonas JB, Zach FM, Gusek GC, et al. Pseudoglaucomatous physiologic large cups. Am J Ophthalmol. 1989;107(2):137–44.
59. Lichter PR. Variability of expert observers in evaluating the optic disc. Trans Am Ophthalmol Soc. 1976;74: 532–72.
60. Carpel EF, Engstrom PF. The normal cup-disk ratio. Am J Ophthalmol. 1981;91(5):588–97.
61. Varma R, Steinmann WC, Scott IU. Expert agreement in evaluating the optic disc for glaucoma. Ophthalmology. 1992;99(2):215–21.
62. Garway-Heath DF, Ruben ST, Viswanathan A, et al. Vertical cup/disc ratio in relation to optic disc size: its value in the assessment of the glaucoma suspect. Br J Ophthalmol. 1998;82(10):1118–24.
63. Healey PR, Mitchell P, Smith W, et al. Relationship between cup-disc ratio and optic disc diameter: the Blue Mountains Eye Study. Aust N Z J Ophthalmol. 1997;25 Suppl 1:S99–101.
64. Jonas JB, Budde WM, Panda-Jonas S. Ophthalmoscopic evaluation of the optic nerve head. Surv Ophthalmol. 1999;43(4):293–320.
65. Varma R, Tielsch JM, Quigley HA, et al. Race-, age-, gender-, and refractive error-related differences in the normal optic disc. Arch Ophthalmol. 1994;112(8): 1068–76.
66. Tielsch JM, Sommer A, Katz J, et al. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA. 1991;266(3): 369–74.
67. Mason RP, Kosoko O, Wilson MR, et al. National survey of the prevalence and risk factors of glaucoma in St. Lucia, West Indies. Part I. Prevalence findings. Ophthalmology. 1989;96(9):1363–8.
68. Mardin CY, Horn FK. Influence of optic disc size on the sensitivity of the Heidelberg Retina Tomograph. Graefes Arch Clin Exp Ophthalmol. 1998;236(9): 641–5.
69. Funaki S, Shirakashi M, Abe H. Relation between size of optic disc and thickness of retinal nerve fibre layer in normal subjects. Br J Ophthalmol. 1998; 82(11):1242–5.
70. Piette SD, Sergott RC. Pathological optic-disc cupping. Curr Opin Ophthalmol. 2006;17(1):1–6.
71. Trobe JD, Glaser JS, Cassady J, et al. Nonglaucomatous excavation of the optic disc. Arch Ophthalmol. 1980;98(6):1046–50.
72. Greenfield DS, Siatkowski RM, Glaser JS, et al. The cupped disc. Who needs neuroimaging? Ophthalmology. 1998;105(10):1866–74.

IOP: The Importance of Intraocular Pressure

8

Douglas R. Anderson

Core Messages

- IOP contributes to damage of the optic nerve in glaucoma, but an elevated IOP is not itself the defining feature of glaucoma.
- For diagnosis of glaucoma, the level of the IOP is not of overriding importance although an abnormal IOP makes the diagnosis more certain.
- Current treatment of glaucoma is aimed at lowering the IOP based on evidence from clinical trials.
- Non-IOP factors determine the level of IOP that will be tolerated and explain cases of progressive glaucoma with the IOP in the normal range.
- The prime criterion that determines whether or not therapy is adequate is the stability of the optic nerve and visual function, not the IOP levels.

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8.1 Why Is Intraocular Pressure Important in Diagnosing and Treating Glaucoma?

8.1.1 High IOP Can Cause Glaucoma Although High IOP Itself Is Not Glaucoma

In patients with an anatomic or pathophysiologic condition of the optic nerve that makes it susceptible to glaucoma, intraocular pressure (IOP) level affects whether the optic nerve is damaged and the rate at which that damage occurs. Clinical trials published in the last three decades have confirmed that if IOP is lowered, an eye with ocular hypertension is less likely to develop glaucoma and has a slower rate of visual field deterioration [7, 14]. In trials of established glaucoma with or without abnormally high IOP, progression of disc damage and field loss is slowed or halted by lowering IOP [2, 10, 13, 18].

The proportion of individuals with glaucomatous damage increases with increasing levels of IOP. The proportion of those with "normal" pressure who have glaucoma is small. Yet, most individuals with glaucoma have IOP "in the normal range." The small proportion with glaucoma among the large number with "normal" IOP accounts for one-third to one-half of all cases of glaucoma. The proportion of eyes with glaucoma increases gradually with higher and higher pressure, but not until the IOP reaches 35 mmHg does the proportion with glaucoma reach 50 % [4].

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Thus, a low IOP does not guarantee glaucoma is absent, but a high pressure also doesn't make glaucoma likely until the IOP is considerably elevated. Thus, the level of IOP in itself is a poor means to detect those who have optic nerve damage or visual field loss.

8.1.2 Glaucoma Is Diagnosed Independently of IOP

Glaucoma is diagnosed when there are characteristic changes to the optic nerve and visual function. This pathologic process can occur at any level of IOP. Glaucoma is recognized during clinical examination of the optic disc by the tendency for localized loss of tissue in the neuroretinal rim, most often at the superior and inferior poles of the disc [1, 9, 12, 15]. If the anatomy appears pathological, visual field tests can help to confirm the diagnosis. It is not unusual, however, for a slightly damaged optic nerve to have an entirely normal visual field, or for unrecognized optic disc abnormalities to be associated with mild but definite glaucomatous field loss. Sometimes with early glaucoma, noting a *change* in structure or function from previous examinations is more helpful in making the diagnosis of glaucoma than the disc or visual field appearance on a single examination. Therefore, if there is reason to think the person is at risk of having subclinical glaucoma, or is at risk of developing glaucoma, baseline conditions of the disc, visual field, and other relevant features that can be quantified are recorded and placed in the medical record.

8.1.3 Non-IOP Factors Are Involved in the Pathogenesis of Glaucoma

Individual variation in the magnitude of pressure susceptibility is evident from the fact that some individuals suffer little harm from an abnormally high IOP (ocular hypertension), while others have damage with IOP within the normal range (normal tension glaucoma, or NTG). However, as already noted, there is a gradation of susceptibility, with an increasing proportion of eyes developing glaucoma as IOP rises from the normal range into the 20s, rising to half of eyes in population studies with an IOP of 35 mmHg having glaucoma [4]. Above that level the risk is even higher, with only a few eyes able to withstand pressures between 40 and 50 mmHg. Pain or corneal edema may develop and be a pressing reason for treatment even if the optic nerve has not yet been damaged.

While the pathophysiologic process of glaucomatous cupping is not understood, a working hypothesis is that it results from an interplay between IOP and various physiological processes that vary from one person to another. For example, vasoconstriction that limits regulation of blood flow in the optic disc may be an etiologic factor in glaucoma. The amount of vasoconstriction with exposure to cold ("vasospasm") may vary from one individual to another. To the degree that such a variation in physiologic response participates in the pathophysiologic process of glaucoma, it is logical that if a person has glaucoma with a lower level of IOP, he may be more likely to be at one extreme of the spectrum of the relevant pathophysiologic processes than a person with "high-pressure" glaucoma. Stated differently, without the fundamental disease being different, the non-IOP contributing factors may be more conspicuous in patients with a normal IOP, and inconspicuous in those with no damage in the face of considerably elevated IOP.

Summary for the Clinician

- IOP contributes to the development and progression of glaucoma
- Non-IOP factors also contribute to the etiology of glaucoma and must be considered
- IOP does not define glaucoma
- For the diagnosis of glaucoma, the level of IOP is unimportant although in equivocal cases an abnormal IOP makes the diagnosis of glaucoma more certain
- There are individual differences in the magnitude of pressure susceptibility

8.2 How Much Should IOP Be Lowered?

In patients with established glaucoma, the treatment is to lower the IOP. The goal is to lower IOP to a level at which nerve damage and field loss is halted, or at least slowed. The amount required to achieve this goal is uncertain, but some guidelines have been developed [11]: 40 % (or sometimes 50 %) lowering for cases with severe damage, 30 % for those with moderate damage, and 20 % (or 25 %) for mild damage. Such rules help to establish a soft preliminary pressure target; the IOP goal is lowered if further disc or field progression is seen to occur at the preliminary goal. On the other hand, if the IOP goal is not quite reached with safely tolerated treatment, a lesser goal might be accepted for the moment, given the uncertainty of the guidelines and the variation from one person to another. Progression is typically slow, so it may take diligent monitoring for many years until it can be assessed whether the rate of deterioration (if any) is worrisome enough to warrant more aggressive treatment.

Summary for the Clinician

- A preliminary IOP target range should be set based on severity of glaucoma
  - The target should be adjusted if progression occurs

8.3 How Should IOP Be Used in Monitoring a Patient with Glaucoma?

The IOP measurement is a surrogate or short-term predictor of what the future likely holds. Usually, if the treated IOP is substantially lower than it was before treatment, the course of events will be better than if treatment had not been undertaken. As IOP fluctuates from one time to another, it is best to obtain several baseline readings (rather than a single baseline reading) to obtain an average for comparison to a future set of readings as a guide to adequacy of therapy. The tonometric reading need not be corrected for corneal thickness during long-term monitoring; if the uncorrected tonometric reading is lower, it can be assumed that the actual IOP is equivalently lowered. Thus, corneal thickness is a component of estimating risk before glaucoma develops, but has not been shown useful for making judgment about the risk of progression. (See Chap. 10 for discussion of CCT and IOP.)

Office measurements of IOP are not truly representative of the IOP that an eye experiences. For example, considerable variation in IOP may occur that is not detected at the limited number of office pressure measurements, or the patient may not take medications regularly but does so on the day of an office visit. The initial goal set for IOP lowering may not have been set adequately low, and with time, despite a seemingly satisfactory IOP, the glaucoma progresses. If this happens, the IOP goal needs to be reset to a lower level. It is wise to query the patient about adherence to medications prescribed and to emphasize their importance in the face of deterioration. However, it can be notoriously difficult to obtain an accurate assessment of adherence. For these reasons, IOP measurements alone are not enough to monitor a patient with glaucoma. What the IOP measurements do provide is some short-term gauge about what to expect long term, even though the future cannot be predicted accurately.

It is useful to keep track of IOP readings during the initial months of treatment, which may later be the baseline for setting a new, lower future IOP goal if unexpected progression occurs. IOP measurements are also immediately useful when a target IOP goal has been set and treatment does not achieve the pressure goal that was thought necessary to slow or halt the disease. In addition, if the IOP lowering is very disappointing compared to the pressure before treatment, one need not wait until the disc and field deteriorate to reach the decision that a different approach is needed in an effort to lower the IOP even more.

Summary for the Clinician

- In monitoring a patient, the stability or change in the condition of the optic nerve and visual function is the prime criterion for whether IOP-lowering therapy is adequate
- Because glaucomatous damage will either halt or slow when IOP is lowered, treatment is aimed at lowering the IOP

8.4 Should IOP Be Treated If It Is Only a Risk Factor?

The IOP may be high and not have caused harm. With time some eyes will develop structural or functional glaucomatous damage. In the long term, more people with a normal nerve will NOT develop glaucoma than will develop it if there has been chronic sustained IOP elevation. However, there are markers that will help identify an increased risk of glaucoma in eyes with abnormal IOPs. Age is prime among them, as well as the level of IOP. As shown in the Ocular Hypertension Treatment Study (OHTS) [6], age up to 80 years and untreated pressure between 20 and 32 mmHg incur risk for some, but intuitively an even greater age or higher IOP would increase the risk even more. A thin cornea also increases the risk, explained partly but probably not entirely, by underestimation of IOP by tonometry [5, 6]. The degree of risk is usually small, and any calculated risk is a risk of developing "just detectable" glaucoma, and the delay in starting treatment is of little consequence [14]. There is therefore little benefit of preventive treatment of ocular hypertension in general, but some small but measurable benefit for those at high risk. There is no benefit to those at low risk [8]. In population studies, at any age the number of individuals with "ocular hypertension" far exceeds the number with fully manifest glaucoma [4].

Evidence that glaucoma may have begun is also a risk factor for developing unequivocal glaucoma. Such evidence may be found in visual fields as an abnormal Pattern Standard Deviation (PSD) index (or for the Octopus perimeter abnormal corrected loss variance). Similarly, this kind of evidence can be found in the disc evaluation. For example, with a vertical cup–disc ratio of 0.8 or more, or any localized thinning of the rim, especially and most typically near the upper or lower poles of the disc. Of note, such localized thinning of the rim is noteworthy even if the cup–disc ratio does not reach 0.8 [1, 9, 15]. Abnormalities in the disc that are suggestive and predictive may also be found in quantitative imaging of the optic disc [19].

There are risk calculators based on the findings of the OHTS. They make the estimate of risk more consistent among doctors. Doctors and patients may decide to start treatment if the risk is above 25 or 50 %, but it must be kept in mind that the risk so calculated is the risk of developing a small increment of disc change or field loss. Treatment started in the minority of ocular hypertensive individuals after they develop early glaucoma will slow the progression of field loss just as adequately as if treatment had been started from prophylactically [14].

Economic analyses, which can take into account the dollar-value of such things as worry about going blind and relief from worry, confirm that it does make sense to treat certain individuals with abnormal IOP [16, 17], especially those who are more concerned about the consequences of elevated pressure than they are about the risk of treatment side effects. However, if easily tolerated treatment is not effective in lowering the IOP, the situation should be revisited with the patient before undertaking more aggressive and risky treatment. On the other hand, for those patients who do not wish to have treatment unless it is absolutely necessary, it may be very appropriate to monitor them regularly (more frequently at first, less frequently later) rather than urge them to have IOP-lowering therapy that on their own they may decide not to use. Therefore, the decision to lower IOP as prevention remains part of the art of medicine, which takes into account the personality, fears, socioeconomic circumstances,

and attitudes of patients toward preventative care as well as the prediction of medical outcome. These considerations seem more important than the calculated risk of developing barely detectable glaucoma before starting treatment.

A common question is, "at what level of IOP would one treat a patient who shows no evidence of damage to the optic nerve or loss of visual function, and no other risk factors?" The historical approach here is to lower the IOP simply because it is abnormal and it is a known risk factor, and in more recent years some arbitrary IOP (e.g., 30 mmHg) begins to concern the doctor in the same way that a pressure over 20 mmHg did in the past. However, any arbitrary number fails to take into account other contributions to glaucoma risk. It may even be reasonable not to start treatment at any pressure unless there is (1) some evidence suggesting early disc damage, (2) suggestive but uncertain signs of early field loss, or (3) symptoms, such as pain and visual effects from corneal edema as the pressure approaches or exceeds 50 mmHg. An exception is when there is a recently elevated IOP, for example, from blunt trauma or anterior uveitis. Elevation of pressure from the teens to 25 mmHg can cause rapid cupping and field loss over only 10 or 20 days. Perhaps treatment is not needed, but close monitoring is required. Another exception to the policy of watchful waiting is emerging closure of the anterior chamber angle. The formation of synechiae that become firmly adherent to the meshwork will eventually result in a steady rise of pressure that will be harmful and is likely to require surgical treatment. Prompt intervention, even without disc or visual field abnormality, is warranted.

In cases of mild glaucoma with *normal* IOP, the use of treatment is discretionary (determined by aversion of the patient to any risk of glaucoma progression or aversion to unnecessary treatment). There is evidence that only half of untreated patients with NTG will manifest progression in 7 years of follow-up [3]. In those who progress, however, treatment is of benefit to most [2].

Summary for the Clinician

- At present, the susceptibility factors are not known, and current therapy toward such factors that may be suspected has not been proved of benefit.
- Even if the future risk of glaucoma is based on non-IOP factors, the only modality we currently have available to reduce risk is to lower IOP.

References

1. Anderson DR. The first signs of glaucomatous cupping in the optic nerve [Pierwsze objawy uszkodzenia jaskrowego w nerwie wzrokowym]. Klinika Oczna (Acta Ophthalmologica Polonica). 2011;113(1–3): 82–92.
2. Anderson DR, Drance SM, Schulzer M, Writing committee for Collaborative Normal-tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol. 1998;126:498–505.
3. Anderson DR, Drance SM, Schulzer M, Writing committee for the Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal tension glaucoma. Ophthalmology. 2001;108:247–53.
4. Anderson DR, Hoskins HD. The management of elevated intraocular pressure with normal optic disc and visual fields. Surv Ophthalmol. 1977;21:479–83.
5. Brandt JD, Beiser JA, Kass MA, Gordon MO, Ocular Hypertension Treatment Study (OHTS) Group. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). Ophthalmology. 2001;108: 1779–88.
6. Coleman AL, Gordon MO, Beiser JA, Kass MA, Ocular Hypertension Treatment Study (OHTS). Baseline risk factors for the development of primary open-angle glaucoma in the Ocular Hypertension Treatment Study. Am J Ophthalmol. 2004;138: 684–5.
7. Demirel S, De Moraes CGV, Gardiner SK, Liebmann JM, Cioffi GA, Ritch R, Gordon MO, Kass MA, Ocular Hypertension Treatment Study. The rate of visual field change in the Ocular Hypertension Treatment Study. Invest Ophthalmol Vis Sci. 2012;53:224–7. doi:10.1167/iovs.10-7117.
8. Gordon MO, Gao F, Beiser JA, Miller JP, Kass MA. The 10-year incidence of glaucoma among patients with treated and untreated ocular hypertension. Arch Ophthalmol. 2011;129:1630–1.

9. Harizman N, Oliveira C, Chiang A, et al. The ISNT rule and differentiation of normal from glaucomatous eyes. Arch Ophthalmol. 2006;124:1579–83.
10. Heijl A, Leske MD, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Ophthalmol. 2002;120:1268–79.
11. Hodapp E, Parrish RK, Anderson DR. Clinical decisions in glaucoma. St Louis: Mosby; 1993. p. 66–7 [1993 first edition out of print, but second edition expected soon].
12. Jonas JB, Gusek GC, Naumann GO. Optic disc, cup and neuroretinal rim size, configuration, and correlations in normal eyes. Invest Ophthalmol Vis Sci. 1988;29:1151–8 [published corrections appear in Inv Ophthalmol Vis Sci 1991;32:1893 and 1992;32: 474–5].
13. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open angle glaucoma. Arch Ophthalmol. 2002;120:701–13.
14. Kass MA, Gordon MO, Gao F, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JK, Miller JP, Parrish RK, Wilson MR, Ocular Hypertension Treatment Study Group. Delaying treatment of ocular hypertension: The Ocular Hypertension Treatment Study. Arch Ophthalmol. 2010;128:276–87.
15. Kirsch RE, Anderson DR. Clinical recognition of glaucomatous cupping. Am J Ophthalmol. 1973;75: 442–54.
16. Kymes SM, Michael A, Kass MA, et al. Management of patients with ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study (OHTS). Am J Ophthalmol. 2006;141:997–1008.
17. Steward WC, Stewart JA, Nassa QJ, et al. Cost-effectiveness of treating ocular hypertension. Ophthalmology. 2008;115:94–8.
18. The AGIS investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130:429–40.
19. Zangwill LM, Weinreb RN, Beiser JA, Berry CC, Cioffi GA, Coleman AL, Trick G, Liebmann JM, Brandt JD, Piltz-Seymour JR, Dirkes KA, Vega S, Kass MA, Gordon MO. Baseline topographic optic disc measurements are associated with the development of primary open-angle glaucoma: The Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. Arch Ophthalmol. 2005;123:1188–97.

IOP: Instruments to Measure IOP

9

Robert Stamper

Core Messages

- No single tonometer is accurate or usable in all situations.
- Goldmann applanation tonometry is still the most commonly used tonometer.
- Goldmann tonometry becomes less accurate when the cornea is significantly thinner or thicker than average, highly astigmatic, irregular, edematous, or scarred.
- Dynamic contour tonometry is the most accurate tonometer and maintains its accuracy even when the cornea is very thin, edematous, or of irregular curvature.
- Pneumatonometry is somewhat less influenced by corneal thickness than Goldmann tonometry. It is useful in the operating room, in supine and upright positions, and on irregular corneas and provides a real-time paper tracing that helps establish reliability.
- The Tonopen is portable, battery powered, usable in any position and may be especially useful in irregular and scarred corneas or in screening situations where electricity is unavailable or portability trumps accuracy.
- The rebound tonometer (ICare) is battery-powered, portable, and very helpful in patients unwilling or unable to cooperate for other forms of tonometry such as children and patients with dementia. It may also be useful for home tonometry or screening.

9.1 What Is the Brief History of IOP Measurement?

Elevated intraocular pressure (IOP) was first noted to be associated with blindness in the tenth century by an Arabic physician, At-Tabari, and was redescribed in 1622 as being associated with what came to be known as glaucoma by Richard Bannister [1]. Until the late nineteenth century, pressure was estimated by palpation through the eyelid—at best, a way to determine if the IOP is low, medium, high, or very high. A way to actually measure IOP was needed if glaucomatous conditions were to be diagnosed and treated effectively. This is especially true now that efficacy of lowering IOP in both ocular hypertension and glaucoma has been firmly established by large, randomized studies [2–7].

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The most accurate way to measure IOP is to cannulate the eye and directly measure IOP by water column or pressure gauge. For obvious reasons, this approach is not practical for everyday management of glaucoma. All other methods of IOP measurement are indirect. An instrument that purports to measure IOP is called a tonometer. There are basically three different types of tonometers—indentation, applanation, and contour matching. Each of these types of tonometers has potential errors and no single tonometer is good for every situation.

Summary for the Clinician

- The most accurate measure of IOP is through direct cannulation of the eye.
- All other methods of IOP measurement indirectly measure IOP.
- Three types of tonometers exist: indentation, applanation, and contour matching; each has its own set of advantages, disadvantages, and sources of errors.

9.2 What Instrument(s) Most Accurately Measures IOP?

9.2.1 Maklakov Tonometer

The first practical tonometer was the Maklakov tonometer, which was an applanation tonometer. The theory of applanation tonometry comes from the Imbert-Fick law that states the internal pressure of a very thin-walled sphere can be obtained by knowing the force required to flatten (applanate) a known area of the sphere. The Maklakov tonometer has a fixed force (i.e., a weight) and a flat bottom that was smeared with ink; when the tonometer first touched and then flattened the cornea, the ink was transferred to the cornea. The tonometer was then "printed" onto a piece of paper. The area (as determined by the diameter) in the center of the inkblot that was devoid of ink was proportional to the IOP. If the eye moved during the time the tonometer was on the eye, more ink was transferred to the cornea than was necessary due to applanation alone and the IOP was underestimated. Furthermore, for the same reasons that the Goldmann tonometer is inaccurate in thin and thick corneas (see below), the Maklakov suffers from the same source of error. Eyes with corneal irregularity, scarring, edema, or high astigmatism, spread the ink irregularly making it difficult to read the area of applanation. This tonometer was widely used in Europe throughout the last century and still enjoys popularity in Russia and other Eastern European countries.

9.2.2 Schiøtz Tonometry

In 1905, Schiøtz introduced an indentation tonometer in which a plunger with a weight on top was allowed to indent the cornea through a footplate [8]. The depth of indentation gave a good indication of the IOP; the tonometer was calibrated at the factory and needed to be returned to the factory if the calibration was off (Fig. 9.1a). A table is needed to convert the indentation readings to IOP (Fig. 9.1b). Topical anesthetic is required to use this instrument, and the patient had to be in the supine position for the measurement. If the eye moved during the measurement process, corneal abrasion was a possible side effect. Low or high scleral rigidity, outside the average range, introduced a significant error; this was determined by taking a measurement with different weights. These tonometers tended to underestimate the IOP in myopic and young eyes. Any corneal scarring or irregularity invalidated the reading.

9.2.3 Goldmann Tonometry

Goldmann revolutionized tonometry in 1948 with the invention of a variable force, fixed area applanation tonometer whose accuracy surpassed any of the devices preceding it. He predicted that the tonometer's accuracy would be affected by thick or thin corneas but incorrectly concluded that these would be rare based on his studies of a relatively few eyes in Bern [9, 10]. Because of its presumed accuracy and ease of use, the Goldmann tonometer became the world standard for tonometry within two

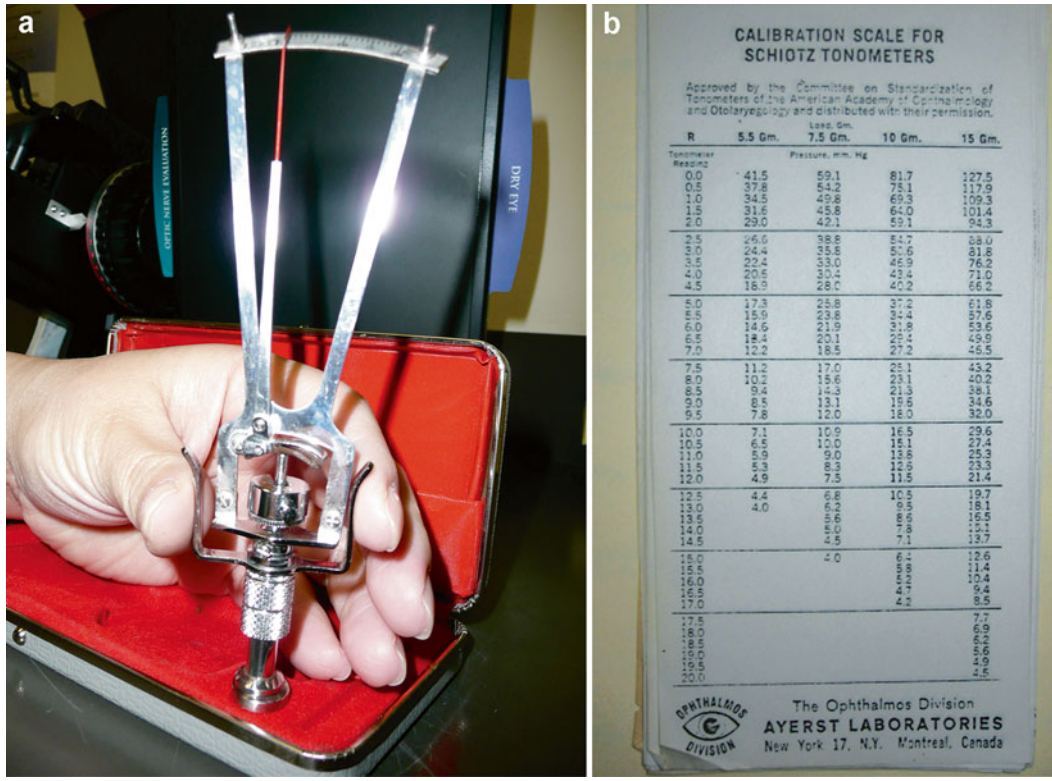

Fig. 9.1 (**a**) Schiøtz tonometer on calibration block. (**b**) Table for converting Schiøtz readings at each weight to intraocular pressure in mmHg

decades of its introduction. While the Goldmann tonometer requires mounting on a slit lamp biomicroscope and an upright subject, modifications by Perkins and Draeger allowed the same principle to be transferred to a portable unit that could be used both in upright and supine positions. Unfortunately, IOP is underestimated significantly by this device (or its modifications) when the cornea is thin or edematous and is overestimated in a thick cornea. Scarring or other surface irregularity prevents a crisp optical endpoint, so accurate IOP determination is difficult if not impossible in such eyes.

9.2.4 Pneumatonometry

The pneumatonometer is basically an applanation device. It uses a column of air to flatten an area of the cornea that is the same as the Goldmann. At the point of applanation, the cornea pushes back on the column of air with a force that equals the force of the air column. A sensor in the device reads the force and is able to calculate the pressure from the force and the known applanation area. The pneumatonometer gives a real-time reading that when graphed on a moving paper shows the pulsatile nature of the IOP. A stable tracing helps to validate a good reading. The pneumatonometer can be used in both the sitting and supine position and, therefore, is useful in determining the difference between upright and supine eye pressures. It is also more accurate than the Goldmann tonometer in irregular, edematous, and scarred corneas [11]. The pneumatonometer can read IOP through a bandage soft contact lens [12]. There is some evidence that it may give a reasonably clinically useable pressure reading from the sclera, which can be helpful if the cornea is very irregular, calcified or in the case of a keratoprosthesis where no other tonometer has been shown to give any useful pressure measurements [13].

9.2.5 McKay–Marg and Tonopen

The next breakthrough in tonometry came from a new hybrid applanation and indentation tonometer developed by McKay and Marg in the late 1950s [15]. In this tonometer, a tiny plunger indents the cornea until the footplate takes the strain off the plunger (the point of applanation). At that point, the gradually increasing force generated by the plunger as read by a strain gauge shows a momentary flattening or reduction. This momentary flattening represents the force necessary to flatten the cornea; this force divided by the area of applanation gives the IOP. Since the endpoint is determined electronically (rather than optically as in the Goldmann), a more precise and presumably accurate reading than with the Goldmann instrument [16] can be obtained in scarred, edematous, and irregular corneas. A portable version using a "smart" chip to calculate the endpoint, the Tonopen, soon followed. The chip also calculates the standard deviation of multiple readings, which serves as a rough measure of consistency and presumed accuracy. The Tonopen can be used in any position, unlike the Schiøtz and Goldmann tonometers, which can only be used in the supine or upright positions, respectively. The Tonopen relates well to Goldmann readings in eyes with "normal" corneas and in the "physiologic" range of IOPs. However, there are some outliers where the Tonopen may differ from the Goldmann by as much as 8 mmHg and accuracy appears to fall off both below 10 mmHg and above 20 mmHg [14, 17, 18]. Being portable and relatively easy to use, the Tonopen can be used for home tonometry to obtain some idea of diurnal or even longer term fluctuation in IOP.

9.2.6 Air-Puff Tonometry

Air-puff tonometers were originally developed to provide a way to measure IOP without the need for topical anesthetic. They are basically applanation tonometers where a column of air of known area is generated at increasing force aimed at the cornea over a very short time (measured in milliseconds) until the cornea is flattened. When the cornea is flattened a light beam is reflected into a sensor, which stops the generation of air and records the force at the moment of applanation. The force divided by the area of applanation is the IOP. It works on the same principle as the Goldmann and Maklakov tonometers. Air-puff tonometers are reasonably accurate over the range of "physiologic" pressures and compare well with Goldmann tonometry [19, 20]. They are particularly useful as screening devices since they do not normally require anesthetic and cannot serve as carriers of pathogens as can tonometers that actually touch the cornea. On the other hand, they are large, not very portable, expensive, and require frequent calibration. Furthermore, they become inaccurate in eyes whose corneas are irregular, scarred, edematous, or astigmatic.

A recent innovation is the Reichert Ocular Response Analyzer (Reichert, Rochester, NY). This is a variant on the air-puff tonometer, which reads the point of applanation like other air-puff tonometers, but in addition further indents the cornea with air pressure and measures the point at which the cornea recovers to applanation. The difference between the first applanation point and the point of recovery is a measure of the biomechanical properties (hysteresis) of the cornea [21]. Abnormal biomechanical properties of the cornea have been associated with both initial and progression of optic nerve damage in glaucoma [22]. Exactly how this can or should be incorporated into the diagnosis and/or management of glaucoma is not clear at this time.

9.2.7 Dynamic Contour Tonometry

A major revolution in the methodology of measuring IOP occurred with the invention by Kanngiesser of the dynamic contour tonometer (DCT). Unlike any of its predecessors, the DCT (Pascal—Zeimer MicroTechnology, Switzerland) does not depend on flattening or indenting the cornea. The basic concept is that the curved tip of the sensor duplicates the curvature of the cornea and the strain gauge located in its center measures a pressure on the outside of the cornea that very closely replicates the pressure on the inside [19] (Fig. 9.2). Accordingly, the device is insignificantly affected by corneal

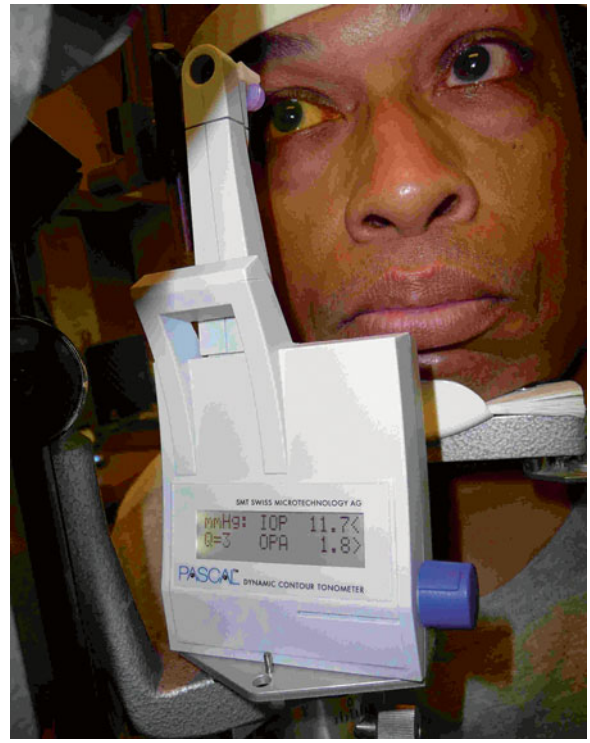

Fig. 9.2 Dynamic contour tonometer mounted on slit lamp. Note digital readout that includes intraocular pressure in mmHg, an indicator of quality (*Q*) with three or more indicating a satisfactory reading and the ocular pulse pressure (*OPA*) in mmHg (the difference between diastolic and systolic intraocular pressure)

thickness, curvature, optical aberrations, or surface irregularity, i.e., it is independent of the errors of applanation and indentation tonometry [23–26]. The DCT appears significantly more accurate both in cadaver and in living eyes than Goldmann tonometry and Pneumatonometry when compared with manometry, even when the cornea is edematous or surgically thinned by LASIK [27–32].

Based on recent evidence, it is clear that the DCT is the most accurate instrument for measuring IOP without significant effect from corneal properties or abnormalities. However, the device is expensive as it is now constituted, can only measure IOP in the upright position, requires topical anesthetic (although no fluorescein is needed), and necessitates a slit lamp to operate. Therefore, it cannot be used in the operating room or at the bedside. It probably is not as useful as some of the other devices in screening situations. Finally, the DCT has not been validated when the corneal curvature is significantly different from physiologic, such as in the early postoperative period for corneal transplants, cornea plana, or buphthalmos.

9.2.8 Rebound Tonometry

Because rodent and other animal eyes are very difficult to applanate using a Goldmann type instrument, researchers developed a tonometer that uses the concept of indentation in a highly sophisticated fashion. In this instrument, a tiny pin with a small ball (1–2 mm diameter) on the tip is driven forward by a magnetic impeller. It hits the cornea and bounces back. The tip touches the cornea for only an instant and is barely felt (topical anesthesia is not necessary). Electronics inside the device measure the time in contact with the cornea and the deceleration as the pin returns to the main unit. The process is analogous to kicking a tire in a used car lot, the softer the tire, the deeper into the tire your foot will sink, and the slower it will bounce back, whereas if the tire is harder (higher pressure) your foot will bounce quickly off the tire. A similar device calibrated for human eyes is now available (ICare, Helsinki, Finland) (Fig. 9.3). Because the reading is almost instantaneous and may catch the IOP at any point in the ocular pulse, there can be significant

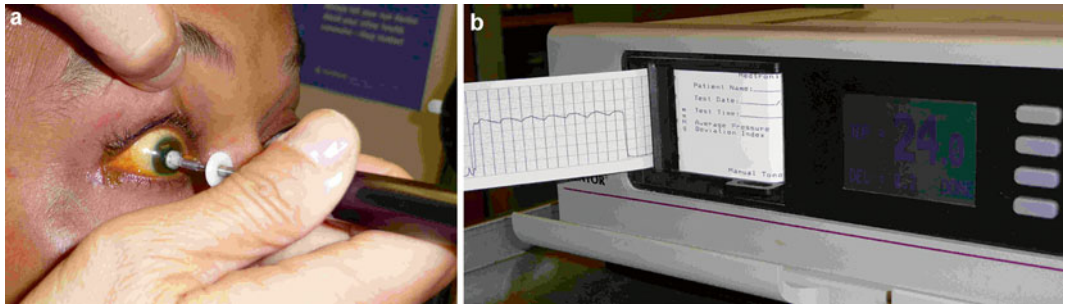

Fig 9.3 (**a**) The pneumatonometer probe on the eye. It floats on a cushion of air. (**b**) The pneumatonometer readout includes a digital average intraocular pressure in mmHg. The paper tracing also indicates the pulsatile nature of intraocular pressure. When the pulses are present and the intraocular pressure is steady, indicates a satisfactory reading

variability (around 8 %) between readings. The company recommends six measurements, which are then averaged and displayed in the digital window. A standard deviation is calculated and the measurement process should be repeated if the standard deviation is elevated. Because the whole process takes a fraction of a second, people who cannot sit still for other forms of tonometry may be measurable with this one. The rebound tonometer correlates well in normal eyes with the Goldmann tonometer [33, 34]. However, sometimes the two instruments come up with clinically significant differences and where the actual IOP resides in these cases is hard to say. The tips are disposable so the risks of transmitting infection are nil. Rebound tonometers have been found to be particularly useful in children, patients with blepharospasm, tight orbit, and uncooperative adults such as those with dementia or mental illness [35, 36]. The newer version of this device can also be used in the supine position, but large-scale validation of the supine measurements is not yet available [37]. Because rebound tonometers are easy to use and require little training, they may be useful for screening and home tonometry [38, 39]; a simplified model specifically for this purpose has been developed.

9.2.9 Trans-Palpebral Tonometers

Recently instruments have been developed that measure IOP through the eyelids; examples include the Proview and the TGDc-01 [40–42]. While these instruments generally are not accurate enough for regular clinical use, they may have some value in approximating IOP when ordinary tonometry is not possible, such as with corneal prostheses and totally scarred corneas.

Summary for the Clinician

- No instrument currently measures IOP accurately under all conditions.
- The Goldmann tonometer is quite accurate in eyes with average corneal thickness.
- In eyes with very thin corneas, either naturally or after LASIK, DCT is the best source of accurate IOP measurement.
- Pneumatonometer also provides reasonably accurate IOP readings across the range of corneal thicknesses and corneal pathology.
- Rebound tonometry is advantageous in children or other minimally cooperative patients.

9.3 If Goldmann Applanation Is Not Available During an Exam Under Anesthesia, What Instrument Is the Next Most Preferred for IOP Measurement?

The Goldmann tonometer cannot measure IOP when the subject is supine. The most accurate way of measuring IOP in the supine position

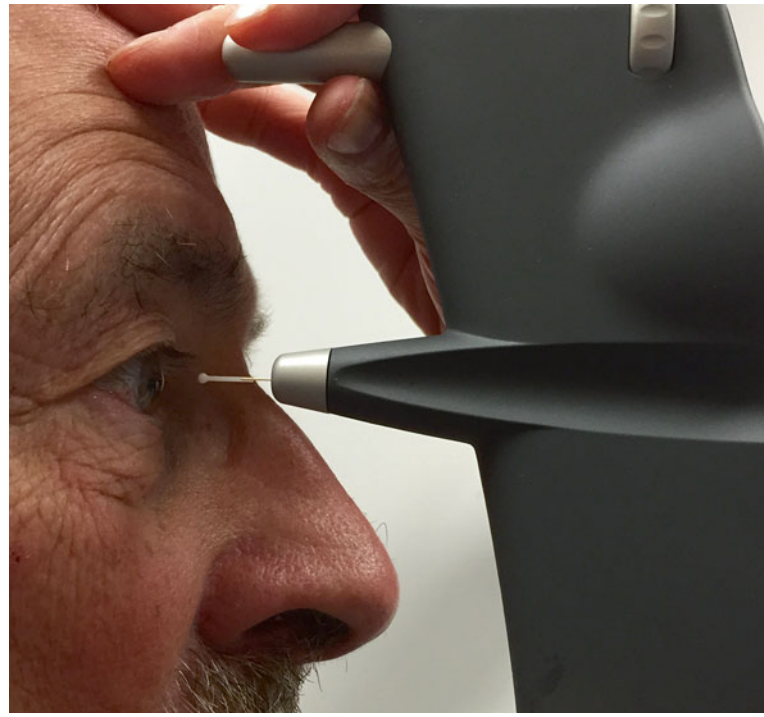

Fig. 9.4 ICare rebound tonometer in use

(as would be true under general anesthesia, under sedation, or at the bedside) is with a Perkins or Draeger tonometer (modified Goldmann-type devices) as long as the cornea is of average thickness and curvature. If the cornea is edematous, thin, thick, or irregular, pneumatonometry would be the most accurate. This is the device used in our own operating room as it works well in almost all circumstances [11] (Fig. 9.4a, b). Somewhat less accurate but still relatively usable is the Tonopen.

Summary for the Clinician

- A portable Perkins or Draeger tonometer is best when measuring average corneas in the supine position.
- Pneumatonometry seems to be the best overall instrument as it is reasonably accurate even when the cornea is abnormal.
- The Tonopen is practical but does not provide the most accurate IOP estimate.

9.4 In Cases of Corneal Transplants, Corneal Edema or Scarring, Which Instrument Would Be Best to Use to Obtain Accurate IOP Measurements?

In eyes with corneal edema, significant surface irregularity, scarring, and recent corneal grafts, pneumatonometry, Tonopen, and DCT will give more accurate readings than Goldmann or other applanation tonometry. Pneumatonometry may be the most accurate way of measuring IOP in the operating room while the patient is supine. It has the added advantage of giving a printed recording of the real-time pulsatile IOP, the examination of which can confirm or question whether the reading is likely to be accurate. The Tonopen also may be useful in the operating room or at the bedside. If multiple readings are taken, the instrument records a standard deviation, which is an indicator of consistency, and perhaps an indirect indicator of accuracy.

Summary for the Clinician

- Pneumatonometry may best estimate IOP in edematous or scarred corneas and in eyes with corneal transplants.

9.5 In Cases of Prosthetic Corneas How Can I Measure the IOP?

In eyes with totally distorted or calcified corneas and in those with corneal prostheses a scleral reading with the pneumatonometer may be the best way to measure IOP [13]. Palpation or one of the transpalpebral tonometers may also be better than nothing to estimate the IOP.

Summary for the Clinician

- No tonometer will be able to accurately and reliably measure the IOP in the case of a prosthetic cornea. However, a reading from the sclera using the pneumatonometer may be the best way to estimate the IOP in such patients.
- Palpation can be used to estimate IOP as low, medium, or high.

9.6 Can I Convert the Readings of One Instrument to Those of Another?

While some have tried to apply a conversion factor to Goldmann readings, especially as they apply to corneal thickness, the lack of linearity in the relationship between corneal thickness and Goldmann readings has made it impossible for any single conversion factor to take an inaccurate reading and make it accurate. The errors of the other instruments are also nonlinear, and therefore conversion cannot be made from one instrument to the next.

Summary for the Clinician

- Each instrument has its own nonlinear margin of error.
- At the present time, we don't know what conversion factor(s) would have to be used between different instruments.

References

1. Damji K, Epstein D. History of outflow resistance. In: Van-Buskirk M, Shields B, editors. 100 years of progress in glaucoma. Philadelphia: Lippincott-Raven; 1997.
2. Collaborative Initial Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol. 1998;126:498–505.
3. AGIS (Advanced Glaucoma Intervention Study) Investigators. 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000;130:429–40.
4. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Ophthalmol. 2002;120:1268–79.
5. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701–13; discussion 829–30.
6. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108:1943–53.
7. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121:48–56.
8. Schiøtz H. Ein neues Tonometer. Arch f Augenh 1905;LII:part IV.
9. Goldmann H. Un nouveau tonometre d'applanation. Bull Soc Ophtalmol Fr. 1955;67:474–8.
10. Goldmann H, Schmidt T. On applanation tonography. Ophthalmologica. 1965;150(1):65–75.
11. Eisenberg DL, Sherman BG, McKeown CA, Schuman JS. Tonometry in adults and children. A manometric evaluation of pneumatonometry, applanation, and TonoPen in vitro and in vivo. Ophthalmology. 1998;105(7):1173–81.
12. Mark LK, Asbell PA, Torres MA, Failla SJ. Accuracy of intraocular pressure measurements with two different

tonometers through bandage contact lenses. Cornea. 1992;11(4):277–81.
13. Lin CC, Chen A, Jeng BH, Porco TC, Ou Y, Han Y, et al. Scleral intraocular pressure measurement in cadaver eyes pre- and postkeratoprosthesis implantation. Invest Ophthalmol Vis Sci. 2014;55(4): 2244–50.
14. Augsburger A, Terry JE. Non-contact and Mackay-Marg tonometry: comparison in patients ages 7 to 85 years. Am J Optom Physiol Opt. 1977;54(1): 31–4.
15. MacKay RS, Marg E. Fast, automatic, electronic tonometers based on an exact theory. Acta Ophthalmol Scand Suppl. 1959;37:495–507.
16. Kaufman HE, Wind CA, Waltman SR. Validity of Mackay-Marg electronic applanation tonometer in patients with scarred irregular corneas. Am J Ophthalmol. 1970;69(6):1003–7.
17. Frenkel RE, Hong YJ, Shin DH. Comparison of the Tono-Pen to the Goldmann applanation tonometer. Arch Ophthalmol. 1988;106(6):750–3.
18. Kao SF, Lichter PR, Bergstrom TJ, et al. Clinical comparison of the Oculab Tono-Pen to the Goldmann applanation tonometer. Ophthalmology. 1987;94(12): 1541–4.
19. Forbes JM, Pico GJ, Grolman B. A non-contact applanation tonometer. Description and clinical evaluation. Arch Ophthalmol. 1974;91(2):134–40.
20. Moseley MJ, Thompson JR, Deutsch J, et al. Comparison of the Keeler Pulsair 2000 non-contact tonometer with Goldmann applanation. Eye. 1993;7 (Pt 1):127–30.
21. Luce DA. Determining in vivo biomechanical properties of the cornea with an ocular response analyzer. J Cataract Refract Surg. 2005;31(1):156–62.
22. Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol. 2006;141(5):868–75.
23. Kanngiesser H, Kniestedt C, Robert YC. Dynamic contour tonometry: presentation of a new tonometer. J Glaucoma. 2005;14(5):344–50.
24. Kniestedt C, Punjabi O, Lin S, Stamper R. Tonometry through the ages. Surv Ophthalmol. 2008;53(6): 568–91.
25. Duba I, Wirthlin AC. Dynamic contour tonometry for post-LASIK intraocular pressure measurements. Klin Monbl Augenheilkd. 2004;221(5):347–50.
26. Kampetter BA, Jonas JB. Dynamic contour tonometry for intraocular pressure measurement. Am J Ophthalmol. 2005;140(2):318–20.
27. Kaufmann C, Bachmann LM, Thiel MA. Intraocular pressure measurements using dynamic contour tonometry after laser in situ keratomileusis. Invest Ophthalmol Vis Sci. 2003;44(9):3790–4.
28. Kniestedt C, Lin S, Choe J, et al. Clinical comparison of contour and applanation tonometry and their relation to pachymetry. Arch Ophthalmol. 2005;123(11): 1532–7.
29. Ku JY, Danesh-Meyer HV, Craig JP, et al. Comparison of intraocular pressure measured by Pascal dynamic contour tonometry and Goldmann applanation tonometry. Eye. 2006;20(2):191–8.
30. Kniestedt C, Nee M, Stamper RL. Dynamic contour tonometry: a comparative study on human cadaver eyes. Arch Ophthalmol. 2004;122(9):1287–93.
31. Kniestedt C, Nee M, Stamper RL. Accuracy of dynamic contour tonometry compared with applanation tonometry in human cadaver eyes of different hydration states. Graefes Arch Clin Exp Ophthalmol. 2005;243(4):359–66.
32. Boehm AG, Weber A, Spoerl E, Koch R, Pillunat LE. Dynamic contour tonometry in comparison to intracameral IOP measurements. Invest Ophthalmol Vis Sci. 2008;49(6):2472–7.
33. Sinha G, Gupta S, Temkar S, Pandey V, Sihota R, Dada T. IOP agreement between I-Care TA01 rebound tonometer and the Goldmann applanation tonometer in eyes with and without glaucoma. Int Ophthalmol. 2014 Dec 16 [Epub ahead of print].
34. Smedowski A, Weglarz B, Tarnawska D, Kaarniranta K, Wylegala E. Comparison of three intraocular pressure measurement methods including biomechanical properties of the cornea. Invest Ophthalmol Vis Sci. 2014;55(2):666–73.
35. Dosunmu EO, Marcus I, Tung I, Thiamthat W, Freedman SF. The effect of repeated measurements and the use of topical anesthetic on rebound tonometry values in children. J AAPOS. 2014;18(6):619–21. doi:10.1016/j.jaapos.2014.07.167.
36. Lee YK, Lee JY, Moon JI, Park MH. Effectiveness of the ICare rebound tonometer in patients with overestimated intraocular pressure due to tight orbit syndrome. Jpn J Ophthalmol. 2014;58(6):496–502.
37. Schweier C, Hanson JV, Funk J, Töteberg-Harms M. Repeatability of intraocular pressure measurements with Icare PRO rebound, Tono-Pen AVIA, and Goldmann tonometers in sitting and reclining positions. BMC Ophthalmol. 2013;13:44.
38. Moreno-Montañés J, Martínez-de-la-Casa JM, Sabater AL, Morales L, Sáenz C, Garcia-Feijoo J. Clinical evaluation of the New Rebound Tonometers Icare PRO and Icare ONE compared with the Goldmann Tonometer. J Glaucoma. 2015;24(7):527–32.
39. Sakamoto M, Kanamori A, Fujihara M, Yamada Y, Nakamura M, Negi A. Assessment of IcareONE rebound tonometer for self-measuring intraocular pressure. Acta Ophthalmol. 2014;92(3):243–8.
40. Meyer MW, Gockeln R, Hoy L, Meyer A, Erb C. Comparison of intraocular pressure measurements with the digital tonometer TGDc-01 'PRA' and the Goldmann applanation tonometer. Ophthalmic Res. 2004;36(5):250–4.
41. Troost A, Specht K, Krummenauer F, et al. Deviations between transpalpebral tonometry using TGDc-01 and Goldmann applanation tonometry depending on the IOP level. Graefes Arch Clin Exp Ophthalmol. 2005;243(9):853–8.
42. Troost A, Yun SH, Specht K, et al. Transpalpebral tonometry: reliability and comparison with Goldmann applanation tonometry and palpation in healthy volunteers. Br J Ophthalmol. 2005;89(3):280–3.

IOP: Central Corneal Thickness

10

James D. Brandt

Core Messages

- Variations in central corneal thickness (CCT) influence the accuracy of all tonometry techniques to some degree.
- The Ocular Hypertension Treatment Study demonstrated that CCT is an independent predictive factor for the later development of glaucoma among ocular hypertensives, with thinner CCT conferring increased glaucoma risk; this finding was externally verified in the European Glaucoma Prevention Study.
- The evidence that CCT is an independent risk factor for progression in established glaucoma is weaker than for glaucoma conversion in ocular hypertension, but ongoing studies will likely clarify this relationship.
- CCT is an inherited ocular characteristic and appears to change little during adulthood in otherwise healthy eyes. On average, CCT decreases by a few microns per decade of life.
- Nomograms for "correcting" IOP measurements with CCT are not valid in individual patients and should not be used clinically. The influence of other factors such as corneal hydration and viscoelasticity probably dwarf the impact of CCT on IOP measurements.
- On average, measured IOP drops following all forms of keratorefractive surgery, but there are substantial numbers of patients in whom IOP rises, so the use of a fixed nomogram based on CCT, refractive correction, or laser ablation should not be used.

10.1 Why Has Central Corneal Thickness Become So Important?

10.1.1 Goldmann Tonometry

Ever since the recognition that glaucoma was associated in many patients with a firm eye, ophthalmologists have been attempting to measure intraocular pressure (IOP) clinically. Prior to the introduction of Goldmann Applanation Tonometry (GAT) in the 1950s, tonometry techniques were inconvenient and unreliable. Professor Goldmann's tonometer rapidly gained widespread acceptance following its introduction—it was reasonably priced, based on easily-understood physical principles, fitted

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seamlessly into the workflow of the slit-lamp exam, and appeared to provide accurate, reproducible measurements. GAT's status as a tonometry "Gold standard" went largely unchallenged for 50 years, even though Professor Goldmann himself drew attention to various potential sources of error for the device in his first description of his tonometer [1]. In particular, Goldmann and Schmidt acknowledged that their design assumptions were based on a central corneal thickness (CCT) of 0.5 mm (500 μm) and that the accuracy of their device would vary if CCT deviated from this value—"Under conditions which differ considerably from our measurement conditions (abnormally thick or thin cornea, for example …), errors of several millimeters are to be expected" [1]. Given the paucity of published data at the time, 500 μm seemed a reasonable assumption for the "average" patient. We now know CCT varies greatly among the general population, to a degree that impacts the accuracy of GAT in daily practice.

10.1.2 The Influence of CCT on Tonometry

The first indication that CCT varied enough in otherwise normal eyes to influence GAT came from Ehlers, who in 1975 cannulated 29 eyes undergoing cataract surgery and correlated CCT to the difference between "true" and GAT-measured IOP [2]. His study demonstrated that GAT error could indeed be as large as 5 or 6 mmHg in otherwise normal eyes, and that GAT appeared most accurate with a CCT of 520 μm. His study had significant limitations, including the relatively small number of patients and (in retrospect) the racial homogeneity of his population; nonetheless, his findings spurred other investigations that suggested that CCT-induced GAT error might be important in ocular hypertension and normal tension glaucoma [3–6]. Unfortunately, the significance of this early work did not gain widespread recognition until the publications of the Ocular Hypertension Treatment Study (OHTS).

Goldmann tonometry measures the force necessary to flatten a fixed area of the central cornea and uses this force to estimate the value of IOP. The forces opposing applanation include both IOP and the structural resistance of the cornea. It seems intuitive that a thicker cornea will resist applanation more than a thin cornea, but the reality is more complex. The structural resistance of the cornea represents a combination of its "stiffness," viscoelastic properties, and thickness. Several engineering models of the cornea suggest that variations in the material properties of the cornea (i.e., viscoelastic properties, Young's modulus—an engineering term for inherent properties) probably dwarf the effect of CCT on GAT measurements [7, 8]. These models suggest that if the material properties of the cornea were constant, variations in CCT from the mid-400s to mid-600s would explain only some ±4 mmHg in variance from "true" (directly measured) IOP, and that variations in material properties may explain ±10 to 15 mmHg in GAT error.

Summary for the Clinician

- Goldmann applanation assumed a constant CCT in the population; however, CCT varies to a degree that impacts the accuracy of the Goldmann applanation.
- Engineering models suggest that material properties of the cornea likely dwarf the effect of CCT on the Goldmann applanation (10–15 mmHg variance from true IOP due to material properties and ±4 mmHg due to CCT).

10.2 How Does Central Corneal Thickness Vary?

10.2.1 CCT in Different Populations

The earliest surveys of corneal thickness were primarily performed in Caucasian Scandinavian populations [9–11]. While these and other early studies demonstrated that CCT varied more within normal populations than previously appreciated, it wasn't until much later that population-based differences were recognized among different racial groups. La Rosa and colleagues

showed that as a group African American male veterans had thinner corneas than their Caucasian counterparts [12] as did African American participants in the OHTS compared to Caucasian participants [13]. The Barbados Eye Survey reported that black participants had thinner corneas than white participants [14]. The population-based Los Angeles Latino Eye Study found CCTs among their Hispanic patients intermediate between values reported for African American and Caucasian populations [15]. What underlies these racial differences? Racial and ethnic categorization is imprecise—there are no genetic alleles that define a unique population or race. On the other hand, the prevalence of certain alleles does vary among populations. Toh et al. in Australia recently showed that CCT is among the most highly heritable aspect of ocular structure [16], suggesting that the gene(s) controlling ocular structure and more specifically corneal thickness may vary among populations.

10.2.2 CCT over Time

CCT appears to hold reasonably steady over time in an individual. Among the largest population and clinical trial-based studies, cross-sectional estimates of time-dependent changes in CCT suggest that on average, CCT either remains unchanged or decreases by up to 0.6 μm/year [13, 14, 17–21]. The only large longitudinal study of time-dependent changes in CCT was performed by the OHTS, which found a rate of corneal thinning of -0.74 ± 3.5 μm/year among its ocular hypertensive participants [22].

Summary for the Clinician

- African Americans tend to have thinner corneas than Hispanics who tend to have thinner corneas than Whites.
- CCT has been reported as the most highly heritable aspect of ocular structure.
- CCT holds steady over time in an individual.

10.3 Does CCT Predict Glaucoma?

10.3.1 Clinical Trials

The importance of CCT in the management of glaucoma patients, particularly those with ocular hypertension, was brought to the forefront by findings from the OHTS [23]. Among the OHTS participants, African American participants had thinner corneas than their Caucasian counterparts, and 25 % of the overall OHTS cohort had CCT values above 600 μm [13]. If one uses Ehler's correction of roughly 7 mmHg/100 μm deviation from the nominal value of 520 μm, then as many as 50 % of OHTS subjects had "corrected" IOP values upon entry ≤21 mmHg! Most dramatically, in the OHTS multivariate model of baseline characteristics predictive of conversion to glaucoma, CCT proved to have the largest impact on glaucoma risk [23]. These findings have been confirmed independently in the European Glaucoma Prevention Study (EGPS) [24, 25], and the merged OHTS/EGPS risk model features CCT as a major component of glaucoma risk [26].

The OHTS and EGPS results suggest that many ocular hypertensive and "glaucoma suspect" patients are being misclassified in terms of glaucoma risk on the basis of erroneous IOP estimates by GAT. Clearly many individuals with elevated GAT measurements but no other findings suggestive of glaucoma probably have normal "true" IOPs and do not need treatment or even increased glaucoma surveillance.

10.3.2 CCT in Established Glaucoma

CCT measurements in patients with diagnosed glaucoma also appear useful; following the OHTS publications, numerous investigators have explored the role of CCT in patients with existing glaucoma, and they have generally found CCT to have a significant impact in these patients as well [27–34]. However, the role of CCT in established glaucoma has not been confirmed as convincingly as for ocular hypertension in prospective, randomized clinical trials. The Early Manifest

Glaucoma Trial (EMGT) initially found no relationship between CCT and either incident glaucoma or glaucomatous progression; with longer follow-up however, the EMGT researchers report a modest relationship between CCT and glaucoma progression, but only for individuals with elevated IOPs [35].

10.3.3 CCT as a Biological Risk Factor

The relationship between CCT and either glaucoma risk or glaucoma progression cannot be explained solely by tonometry artifact. Attempts by the OHTS investigators to adjust IOP data for CCT have failed to eliminate CCT from the risk models. This would suggest that either the published correction algorithms are incorrect, that more than CCT is involved in the tonometry artifact (and thus can't be adjusted away), or perhaps that CCT is linked biologically to glaucoma risk. One intriguing hypothesis is that CCT is linked somehow to the engineering of the optic nerve head. Studies examining the movement of the lamina cribrosa in patients after IOP-lowering intervention have been equivocal [36, 37]. However, the fact that a risk relationship between CCT and glaucoma progression was found in the EMGT—a study in which tonometry played no role in recruitment or treatment—hints at an influence of CCT that is not tonometry related [35, 38].

Summary for the Clinician

- Lower CCT is a risk factor for conversion from ocular hypertension to glaucoma.
- The relationship of CCT and glaucoma progression has not been established.
- Tonometry artifact alone does not explain the relationship between CCT and glaucoma risk.
- CCT may somehow be related to the structure of the optic nerve or lamina cribrosa.

10.4 How Should I Use CCT in Clinical Practice?

10.4.1 Should IOP Be "Adjusted" for CCT?

The enthusiasm with which ophthalmologists embraced pachymetry reflected the belief that they would then be able to "adjust" GAT measurements in individual patients to arrive at a more accurate estimate of IOP. Unfortunately, this approach confuses *accuracy* (how close a measurement is to the true value) with *precision* (the repeatability of a measurement). Clinicians often fail to appreciate the significant *imprecision* of the Goldmann tonometer in most clinical settings—in even the most rigorous settings (e.g., an IOP-focused clinical trial), interobserver GAT precision is approximately ±2.5 mmHg [39]. Compounding this inherent imprecision is the fact that many tonometers in clinical use are out of calibration; a recent survey in the United Kingdom found almost 50 % were out of calibration by >2.5 mmHg after a few months of use [40].

The only way to arrive at an *accurate* estimate with a relatively imprecise device is to take multiple measurements and average the results—the more measurements you acquire, the more likely the average approaches the "true" value (assuming no bias of the underlying technique—this is where CCT and other factors such as viscoelasticity come into play). Thus, applying a "correction" to a single *imprecise* measurement does not lead to a more *accurate* result.

On *average*, thicker corneas lead to erroneously elevated GAT estimates of true IOP, and thinner corneas the opposite. Given the significant variability of tonometry and the underlying CCT-related artifact, "adjusting" a single IOP measurement by a fixed algorithm provides only a false impression of improved accuracy.

10.4.2 Special Situations: Children

The normal distribution of IOP among children appears to be lower than that for adults using GAT [41] and increases with age. The underlying

explanation for this finding is unknown, and may represent changes in underlying physiology (e.g., aqueous humor dynamics) or age-related differences in the biomechanical properties of the cornea (e.g., CCT and viscoelastic properties). The distribution of CCTs appears to mimic that in adults, with children characterized as "ocular hypertensives" having thicker corneas than age-matched normals, and children of African heritage having thinner corneas than their Caucasian counterparts [42]. Children who have undergone surgery for congenital cataract have thicker corneas than phakic controls [43], as do children with aniridia [44].

10.4.3 Special Situations: Refractive Surgery

Following many forms of keratorefractive surgery, including LASIK, LASEK, and PRK, there is a mean decline in measured IOP using Goldmann and Tonopen tonometry [45, 46]. This is true even after surgeries that produce minimal change in CCT, such as radial keratotomy or hyperopic LASIK. IOP measurement by noncontact tonometry appears to result in the largest underestimation of IOP after refractive surgery [47], possibly reflecting large changes in corneal biomechanics and elasticity in addition to changes in corneal curvature.

Chang and Stulting [48] suggest that after myopic LASIK the posterior corneal bed becomes the load-bearing structure during applanation tonometry. Large studies of patients undergoing myopic LASIK indicate that while the *mean* IOP declines, there may be an increase in IOP measurements in a substantial number of patients. These changes in recorded IOP reflect the complexity of corneal biomechanics following keratorefractive surgery, which is the composite of nonuniform regional pachymetry, varied corneal hydration and curvature, as well as altered states of collagen crosslinking. These interindividual differences underlying corneal biomechanics are likely dwarfed further by variations in wound healing from one patient to another.

Using a linear regression model to apply a correction to an individual patient is the wrong way to go. The problem with this approach is clearly illustrated in Fig. 10.1. Although the regression line is statistically significant and demonstrates that *on the average* measured IOP drops after LASIK proportional to the refractive correction, as a clinician you cannot know whether your individual patient lies above or below the regression line.

Studies comparing static (e.g., Goldmann), dynamic (e.g., PASCAL dynamic contour), and the newest form of noncontact tonometry (ocular

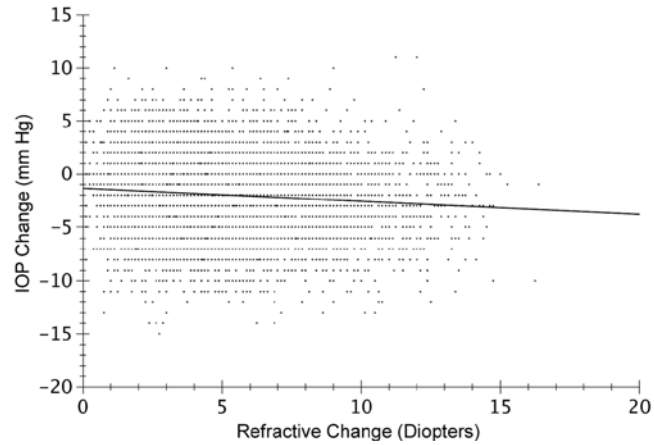

Fig. 10.1 Scatter plot of IOP change after myopic LASIK in over 8000 eyes. The wide variation in IOP change following LASIK shows the futility of using an algorithm derived from a linear regression to "adjust" IOP in an individual patient (from [48])

response analyzer), demonstrate that these two latter forms of tonometry are less sensitive to changes in corneal biomechanics and show small, clinically irrelevant changes following LASIK and LASEK, with less variance than static Goldmann tonometry [49].

10.4.4 Should I Measure CCT in All Patients?

Despite the shift in focus from IOP to the optic nerve in our working definition of glaucoma, tonometry remains the primary glaucoma screening tool used by most eye care practitioners. Unfortunately, elevated IOP is often the first clinical finding that prompts clinicians to look further for the disease. In my opinion ophthalmologists should simply measure CCT in everyone—it takes but a few seconds per eye and can pay dividends in disease detection. As more patients undergo corneal refractive surgery, a growing proportion will have artificially lowered IOP measurements. In a few years, most will neglect to tell their ophthalmologist about their LASIK years ago. We've all seen patients whose glaucoma was detected in an advanced stage because tonometry was "normal" ever since their PRK in the 1980s. This problem will only grow.

If there is one thing I've learned over the past decade of performing pachymetry is that just as it is important to recognize that optic discs are "small, medium, and large" (allowing the clinician to interpret *c*/*d* ratios in context), one can take far better care of patients simply by categorizing corneas as "thin, average, or thick." I have come to define "average" in my practice as being between 520 and 580 μm, and view IOP measurements in patients with CCTs outside this range with an extra dose of skepticism. Trying to be more specific than this is simply not feasible.

Measuring CCT leads to the discontinuation of therapy in many overtreated ocular hypertensives and escalation of therapy in patients with thin corneas where control is clearly inadequate. Ultimately, incorporating the measurement of CCT into the glaucoma exam allows the astute clinician to better target and titrate the treatment of glaucoma.

Summary for the Clinician

- Interobserver GAT precision is ±2.5 mmHg (this is imprecision).
- Many tonometers have been found to be out of calibration.
- Accuracy of GAT is increased by taking multiple measurements and averaging the results.
- Adjusting IOP for the CCT does not provide increased accuracy of the IOP measurement.
- Mean IOP decreases after keratorefractive surgery but a substantial number of patients may have increased IOP after their procedure due to complex changes in corneal biomechanics induced by the surgery.
- CCT should be measured in every glaucoma and glaucoma suspect patient.
- Average CCT lies between 520 and 580 μm.

References

1. Goldmann H, Schmidt T. Über applanationstonometrie. Ophthalmologica. 1957;134:221–42.
2. Ehlers N, Bramsen T, Sperling S. Applanation tonometry and central corneal thickness. Acta Ophthalmol (Copenh). 1975;53(1):34–43.
3. Argus WA. Ocular hypertension and central corneal thickness. Ophthalmology. 1995;102(12):1810–2.
4. Copt RP, Thomas R, Mermoud A. Corneal thickness in ocular hypertension, primary open-angle glaucoma, and normal tension glaucoma [see comments]. Arch Ophthalmol. 1999;117(1):14–6.
5. Ehlers N, Hansen FK. Central corneal thickness in low-tension glaucoma. Acta Ophthalmol (Copenh). 1974;52(5):740–6.
6. Johnson M, Kass MA, Moses RA, Grodzki WJ. Increased corneal thickness simulating elevated intraocular pressure. Arch Ophthalmol. 1978;96(4):664–5.
7. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. J Cataract Refract Surg. 2005;31(1):146–55.
8. Orssengo GJ, Pye DC. Determination of the true intraocular pressure and modulus of elasticity of the human cornea in vivo. Bull Math Biol. 1999;61:551–72.

9. Alsbirk PH. Corneal thickness. I. Age variation, sex difference and oculometric correlations. Acta Ophthalmol (Copenh). 1978;56(1):95–104.
10. Ehlers N, Hansen FK, Aasved H. Biometric correlations of corneal thickness. Acta Ophthalmol (Copenh). 1975;53(4):652–9.
11. Hansen FK. A clinical study of the normal human central corneal thickness. Acta Ophthalmol (Copenh). 1971;49(1):82–9.
12. La Rosa FA, Gross RL, Orengo-Nania S. Central corneal thickness of Caucasians and African Americans in glaucomatous and nonglaucomatous populations. Arch Ophthalmol. 2001;119(1):23–7.
13. Brandt JD, Beiser JA, Kass MA, Gordon MO. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). Ophthalmology. 2001; 108(10):1779–88.
14. Nemesure B, Wu SY, Hennis A, Leske MC. Corneal thickness and intraocular pressure in the Barbados eye studies. Arch Ophthalmol. 2003;121(2):240–4.
15. Hahn S, Azen S, Ying-Lai M, Varma R. Central corneal thickness in Latinos. Invest Ophthalmol Vis Sci. 2003;44(4):1508–12.
16. Toh T, Liew SH, MacKinnon JR, Hewitt AW, Poulsen JL, Spector TD, Gilbert CE, Craig JE, Hammond CJ, Mackey DA. Central corneal thickness is highly heritable: the twin eye studies. Invest Ophthalmol Vis Sci. 2005;46(10):3718–22.
17. Aghaian E, Choe JE, Lin S, Stamper RL. Central corneal thickness of Caucasians, Chinese, Hispanics, Filipinos, African Americans, and Japanese in a glaucoma clinic. Ophthalmology. 2004;111(12): 2211–9.
18. Eysteinsson T, Jonasson F, Sasaki H, Arnarsson A, Sverrisson T, Sasaki K, Stefansson E. Central corneal thickness, radius of the corneal curvature and intraocular pressure in normal subjects using non-contact techniques: Reykjavik Eye Study. Acta Ophthalmol Scand. 2002;80(1):11–5.
19. Foster PJ, Baasanhu J, Alsbirk PH, Munkhbayar D, Uranchimeg D, Johnson GJ. Central corneal thickness and intraocular pressure in a Mongolian population. Ophthalmology. 1998;105(6):969–73.
20. Tomidokoro A, Araie M, Iwase A. Corneal thickness and relating factors in a population-based study in Japan: the Tajimi study. Am J Ophthalmol. 2007; 144(1):152–4.
21. Wong TY, Foster PJ, Ng TP, Tielsch JM, Johnson GJ, Seah SK. Variations in ocular biometry in an adult Chinese population in Singapore: the Tanjong Pagar Survey. Invest Ophthalmol Vis Sci. 2001;42(1): 73–80.
22. Brandt JD, Beiser JA, Gordon MO, Lin SC, Alexander MY, Kass MA. Changes in central corneal thickness over time: the Ocular Hypertension Treatment Study. Ophthalmology. 2008;115:1550–6.
23. Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, Parrish II RK, Wilson MR, Kass MA. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):714–20.
24. Miglior S, Pfeiffer N, Torri V, Zeyen T, Cunha-Vaz J, Adamsons I. Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. Ophthalmology. 2007;114(1):3–9.
25. Pfeiffer N, Torri V, Miglior S, Zeyen T, Adamsons I, Cunha-Vaz J. Central corneal thickness in the European Glaucoma Prevention Study. Ophthalmology. 2007; 114(3):454–9.
26. Gordon MO, Torri V, Miglior S, Beiser JA, Floriani I, Miller JP, Gao F, Adamsons I, Poli D, D'Agostino RB, Kass MA. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. Ophthalmology. 2007;114(1):10–9.
27. Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol. 2006;141(5):868–75.
28. Herndon LW, Weizer JS, Stinnett SS. Central corneal thickness as a risk factor for advanced glaucoma damage. Arch Ophthalmol. 2004;122(1):17–21.
29. Hong S, Kim CY, Seong GJ, Hong YJ. Central corneal thickness and visual field progression in patients with chronic primary angle-closure glaucoma with low intraocular pressure. Am J Ophthalmol. 2007; 143(2):362–3.
30. Jonas JB, Stroux A, Velten I, Juenemann A, Martus P, Budde WM. Central corneal thickness correlated with glaucoma damage and rate of progression. Invest Ophthalmol Vis Sci. 2005;46(4):1269–74.
31. Kniestedt C, Lin S, Choe J, Nee M, Bostrom A, Sturmer J, Stamper RL. Correlation between intraocular pressure, central corneal thickness, stage of glaucoma, and demographic patient data: prospective analysis of biophysical parameters in tertiary glaucoma practice populations. J Glaucoma. 2006;15(2):91–7.
32. Medeiros FA, Sample PA, Weinreb RN. Corneal thickness measurements and frequency doubling technology perimetry abnormalities in ocular hypertensive eyes. Ophthalmology. 2003;110(10):1903–8.
33. Medeiros FA, Sample PA, Weinreb RN. Corneal thickness measurements and visual function abnormalities in ocular hypertensive patients. Am J Ophthalmol. 2003;135(2):131–7.
34. Rogers DL, Cantor RN, Catoira Y, Cantor LB, WuDunn D. Central corneal thickness and visual field loss in fellow eyes of patients with open-angle glaucoma. Am J Ophthalmol. 2007;143(1):159–61.
35. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007;114:1965–72.
36. Lesk MR, Hafez AS, Descovich D. Relationship between central corneal thickness and changes of optic nerve head topography and blood flow after

intraocular pressure reduction in open-angle glaucoma and ocular hypertension. Arch Ophthalmol. 2006;124(11):1568–72.
37. Nicolela MT, Soares AS, Carrillo MM, Chauhan BC, LeBlanc RP, Artes PH. Effect of moderate intraocular pressure changes on topographic measurements with confocal scanning laser tomography in patients with glaucoma. Arch Ophthalmol. 2006;124(5):633–40.
38. Brandt JD. Central corneal thickness—tonometry artifact, or something more? Ophthalmology. 2007; 114(11):1963–4.
39. Tonnu PA, Ho T, Sharma K, White E, Bunce C, Garway-Heath D. A comparison of four methods of tonometry: method agreement and interobserver variability. Br J Ophthalmol. 2005;89(7):847–50.
40. Sandhu SS, Chattopadhyay S, Birch MK, Ray-Chaudhuri N. Frequency of Goldmann applanation tonometer calibration error checks. J Glaucoma. 2005;14(3):215–8.
41. Sihota R, Tuli D, Dada T, Gupta V, Sachdeva MM. Distribution and determinants of intraocular pressure in a normal pediatric population. J Pediatr Ophthalmol Strabismus. 2006;43(1):14–8; quiz 36–17.
42. Muir KW, Jin J, Freedman SF. Central corneal thickness and its relationship to intraocular pressure in children. Ophthalmology. 2004;111(12):2220–3.
43. Simon JW, O'Malley MR, Gandham SB, Ghaiy R, Zobal-Ratner J, Simmons ST. Central corneal thickness and glaucoma in aphakic and pseudophakic children. J AAPOS. 2005;9(4):326–9.
44. Brandt JD, Casuso LA, Budenz DL. Markedly increased central corneal thickness: an unrecognized finding in congenital aniridia. Am J Ophthalmol. 2004;137(2):348–50.
45. Agudelo LM, Molina CA, Alvarez DL. Changes in intraocular pressure after laser in situ keratomileusis for myopia, hyperopia, and astigmatism. J Refract Surg. 2002;18(4):472–4.
46. Faucher A, Gregoire J, Blondeau P. Accuracy of Goldmann tonometry after refractive surgery. J Cataract Refract Surg. 1997;23(6):832–8.
47. Hjortdal JO, Moller-Pedersen T, Ivarsen A, Ehlers N. Corneal power, thickness, and stiffness: results of a prospective randomized controlled trial of PRK and LASIK for myopia. J Cataract Refract Surg. 2005;31(1):21–9.
48. Chang DH, Stulting RD. Change in intraocular pressure measurements after LASIK the effect of the refractive correction and the lamellar flap. Ophthalmology. 2005;112(6):1009–16.
49. Pepose JS, Feigenbaum SK, Qazi MA, Sanderson JP, Roberts CJ. Changes in corneal biomechanics and intraocular pressure following LASIK using static, dynamic, and noncontact tonometry. Am J Ophthalmol. 2007;143(1):39–47.

IOP: Corneal Hysteresis

11

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Core Messages

- Corneal hysteresis (CH) is a measurement that reflects the viscoelastic properties of the cornea and gives an indication of its biomechanical integrity.
- Large variations from normal values for CH can profoundly affect the measurement of intraocular pressure (IOP).
- Central corneal thickness (CCT) and CH values are independently associated with under- and overestimation of IOP. Therefore, CCT and CH are important clinical parameters for the clinician to consider when estimating true IOP.
- The dynamic contour tonometer estimates IOP most independently of CCT and is ideal for use in LASIK-thinned corneas.

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11.1 What Is Corneal Hysteresis and How Does it Influence IOP Measurement?

Corneal hysteresis (CH) is a measurement that reflects the viscoelastic properties of the cornea and its biomechanical integrity. Hysteresis is expressed in units of mmHg, just like intraocular pressure (IOP). Unlike IOP, CH shows no significant variation throughout the day [1]. The Ocular Response Analyzer (ORA) (Reichert Corp. Buffalo, NY) is an instrument that measures CH. It uses a rapid air pulse to record two applanation pressures (Fig. 11.1) [2]. One applanation pressure is recorded while the cornea is moving inward, during indentation, and the second is measured while the cornea is moving outward (while recovering from indentation). The difference between the two pressures is CH. These two pressures are different because of corneal resistance properties delaying the inward and outward applanation.

IOP, on the other hand, is derived indirectly from a force measurement and is based on a number of assumptions about corneal deformability. Corneal deformability represents a summation of the actual IOP, surface tension, the cornea's curvature, and elastic properties [3]. The cornea's elasticity is affected by many properties, including its thickness, collagen composition, and packing density of collagen fibrils, hydration, and extracellular matrix among other factors that undoubtedly vary from individual to individual.

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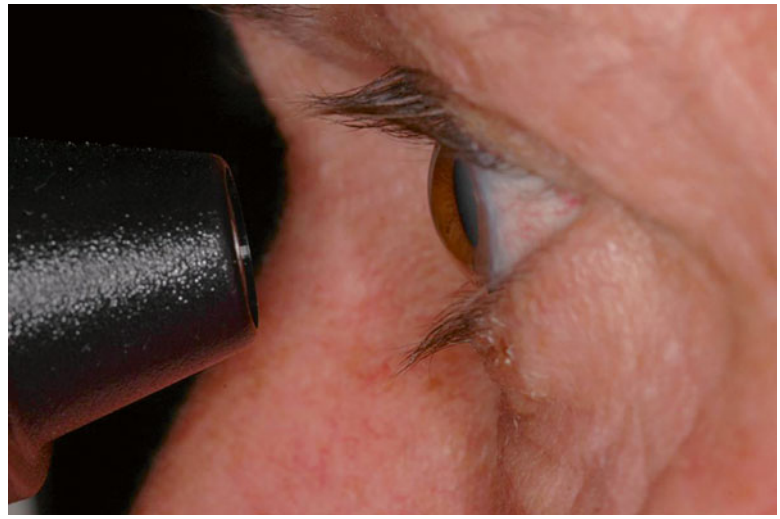

Fig. 11.1 The ocular response analyzer (Reichert Corp.). From teaching files of Leon Herndon

The corneal properties just listed may dwarf the effect of CCT on the accuracy of IOP estimation.

In a biomechanical model of the cornea, Liu and Roberts demonstrated that corneal biomechanics can have a tremendous impact on IOP [3]. The model uses a value called Young's modulus, also called the modulus of elasticity. Young's modulus is the ratio of stress (load per area) to strain (displacement per unit length) [3]. Materials with higher Young's modulus values are harder to deform than those with lower values, and thus, steel has a higher Young's modulus than that of wood.

Young's modulus values for the human cornea are thought to vary widely, from 0.01 to 10 MPa [3], and there is evidence that refractive surgery can significantly change an individual cornea's value [4]. Significant variations in Young's modulus (i.e., the corneal biomechanics) can have very large effects on IOP measurements. Liu and Roberts used Young's modulus values between 0.1 and 0.9 (which are thought to be physiologic values) in their corneal model while keeping CCT and corneal radius of curvature constant [3]. The difference in predicted IOP measurements was 17 mmHg using 0.1 vs. 0.9 for Young's modulus. This effect was far greater than the effect of CCT or radius of curvature on IOP when Young's modulus was kept constant [3]. There is also evidence to support that a low CH value is a risk factor for underestimation of IOP and that a high CH value is a risk factor for overestimation of IOP [5].

Summary for the Clinician

- Corneal hysteresis is a measurement of the viscoelastic properties of the cornea. It can be likened to the spring effect of the cornea.
- Corneal elasticity is affected by corneal thickness, collagen composition, hydration, and extracellular matrix.
- Corneal hysteresis appears to have a greater effect on measured IOP than on CCT or corneal radius of curvature.
- Corneal hysteresis is measured by the ocular response analyzer.
- Low CH may underestimate IOP and high CH may overestimate IOP.

11.2 What Are Typical Corneal Hysteresis Values?

The average corneal hysteresis in normal eyes has been reported to be 10.7 mmHg in a study by Shah et al. [6] and Carbonaro et al. [7] reported a mean corneal hysteresis among normals of 10.24 mmHg in a large twin study. Patients with primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG) have lower values of CH than do normal patients. A study by Bochmann et al. [8] showed that POAG patients with acquired pit of the optic nerve (APON) had significantly lower CH values compared with those of glaucoma patients without APON (mean CH 8.89 and 10.2 mmHg, respectively). Sullivan-Mee et al. demonstrated that corneal hysteresis was significantly lower in POAG patients than in ocular hypertension, glaucoma suspect, and normal patients [9].

The average CH values of normal children are similar to the values seen in adults (~12.5 mmHg). In pediatric cases of glaucoma, patients have been shown to have lower CH values. A study by Kirwan et al. showed congenital glaucoma patients to have a mean CH of 6.3 mmHg compared with 12.5 mmHg in their normal cohorts [10].

CH values for different ethnic populations are shown in the table below (Haseltine et al. [11]).

	Black	Hispanic	White	*p*-value
CH (mmHg)	8.7 ± 1.6	9.4 ± 1.8	9.8 ± 1.8	<0.001
Mean deviation (dB)	−4.7 ± 6.3	−4.5 ± 6.8	−3.7 ± 6.0	0.54

Summary for the Clinician

- Average normal CH is around 10–12.5 mmHg.
- Normal children have CH values similar to normal adults.
- Decreased CH values are associated with glaucoma.
- African Americans have lower corneal hysteresis than Hispanics and Whites.

11.3 What Is the Relationship Between CCT, IOP, and Corneal Hysteresis?

A great deal of clinical decision making in glaucoma is based around IOP, and we would like to have as accurate a measure of it as possible. It is well known that there are large variations in corneal thickness among individuals, and that corneal thickness can affect pressure readings taken with the Goldmann applanation tonometer (GAT). In their seminal paper, Goldmann and Schmidt [12] acknowledged that when large variations occur in CCT the accuracy of GAT readings can be affected. Corneas that are thicker than normal require greater force to flatten and thinner corneas require less force. This means that thicker corneas yield an overestimation of IOP, whereas thinner corneas give an underestimation. In the 1970s Ehlers et al. [13–15] performed a number of studies assessing the effect of CCT on IOP. They cannulated 29 otherwise normal eyes undergoing cataract surgery and correlated corneal thickness with errors in GAT. They found that GAT most accurately reflected "true" intracameral IOP when CCT was 520 μm, and that deviations from this value resulted in an over- or underestimation of IOP by as much as 7 mmHg per 100 μm.

There is also evidence of a positive correlation between increased CCT and increased CH values [6]. The evidence suggests that thicker corneas possess greater viscoelastic properties,

meaning that they may inherently be less elastic [7]. It has also been noted that increased CH values and CCT are individually associated with less likelihood of glaucomatous disease. A high or low CH value can cause an over- or underestimation of IOP, respectively, the impact of which can be very significant theoretically (see Sect. 11.1). It has been suggested too that corneal biomechanics may reflect the structural integrity of the optic nerve head [16].

Summary for the Clinician

- CCT impacts the accuracy of IOP measurement when taken by GAT, with thicker CCT leading to an overestimation and thinner CCT leading to an underestimation.
- CH impacts the accuracy of IOP measurement; lower CH values are associated with an underestimation of IOP and higher CH values are associated with an overestimation of IOP.

11.4 How Does CH Influence Risk of Glaucoma Progression?

Low corneal hysteresis values have been shown to be significantly associated with glaucoma progression [17–20]. The study by Congdon et al. [17] adjusted for baseline IOP, current IOP, and glaucoma treatment, and found that patients with lower CH had a 0.81 higher probability of visual field progression than those without a low CH score. De Moraes et al. [18] found that eyes that showed visual field progression had lower CH values compared to eyes that did not progress, −7.5 vs. 9.0, respectively.

Various studies have also considered the interdependence of CH with other eye measurement values in progression evaluation. A prospective observational cohort study looking at 114 eyes of patients with glaucoma [19] found that low CH values were associated with a faster rate of visual field loss—each 1 mmHg lower CH measurement was associated with a 0.25 %/year faster rate of visual field decline over time. Introducing a variable for the interaction between CH and IOP then showed that the effect of these two variables on visual field loss was even more complex. In eyes with lower CH values, IOP had a significantly larger impact on rates of visual loss compared with eyes with higher CH. That is, for the eyes with a CH of 5 mmHg, each 1 mmHg higher IOP was associated with a 0.38 %/year faster rate of VFI loss. On the other hand, in the eyes with a CH of 10 mmHg, each 1 mmHg higher IOP was associated with a 0.11 %/year faster rate of VFI loss. The combination of low CH and high IOP was particularly detrimental—an eye with a baseline IOP of 30 mmHg and a CH of 5 mmHg translated to a 30 % decrease in visual field values [19]. CH is also correlated with other signs of glaucomatous damage such as increased optic disc cup depth [20].

While there is no definite explanation for how CH is associated with progression, certain theories have been put forth as possible explanations. The study by Wells et al. [20] found that in patients with glaucoma, optic nerve surface compliance, as measured by increased mean cup depth, was associated with lower corneal hysteresis. In patients with low CH values, medication produces a larger reduction in pressure compared to patients with high CH values [21].

Summary for the Clinician

- Glaucoma patients with lower CH values have greater progressive visual field worsening.
- Low baseline CH is associated with a greater magnitude of IOP reduction following various glaucoma therapies.

References

1. Laiquzzaman M, Bhojwani R, Cunliffe I, et al. Diurnal variation of ocular hysteresis in normal subjects: relevance in clinical context. Clin Experiment Ophthalmol. 2006;34:114–8.
2. http://www.ocularresponseanalyzer.com/how.html

3. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement quantitative analysis. J Cataract Refract Surg. 2005;31: 146–55.
4. Roberts C. Biomechanics of the cornea and wavefront-guided laser refractive surgery. J Refract Surg. 2002;18:S589–92.
5. Touboul D, Roberts C, Kerautret J, et al. Correlations between corneal hysteresis, intraocular pressure, and corneal central pachymetry. J Cataract Refract Surg. 2008;34:616–22.
6. Shah S, Laiquzzaman M, Cunliffe I, et al. Assessment of the biomechanical properties of the cornea with the ocular response analyzer in normal and keratoconic eyes. Invest Ophthalmol Vis Sci. 2007;48:3026–31.
7. Carbonaro F, Andrew T, Mackey DA, et al. The heritability of corneal hysteresis and ocular pulse amplitude: a twin study. Ophthalmology. 2008;115:1545–9.
8. Bochmann F, Ang GS, Azuara-Blanco A. Lower corneal hysteresis in glaucoma patients with acquired pit of the optic nerve (APON). Graefes Arch Clin Exp Ophthalmol. 2008;246:735–8.
9. Sullivan-Mee M, Billingsley SC, Patel AD, et al. Ocular response analyzer in subjects with and without glaucoma. Optom Vis Sci. 2008;85:463–70.
10. Kirwan C, O'keefe M, Lanigan B. Corneal hysteresis and intraocular pressure measurement in children using the Reichert ocular response analyzer. Am J Ophthalmol. 2006;142:990–2.
11. Haseltine SJ, Pae J, Ehrlich JR, et al. Variation in corneal hysteresis and central corneal thickness among black, Hispanic and white subjects. Acta Ophthalmol. 2012;90:626–31.
12. Goldmann H, Schmidt T. Applanation tonometry [German]. Ophthalmologica. 1957;134:221–42.
13. Ehlers N, Hansen FK, Aasved H. Biometric correlations of corneal thickness. Acta Ophthalmol (Copenh). 1975;53:652–9.
14. Ehlers N, Hansen FK. Corneal thickness in low-tension glaucoma. Acta Ophthalmol (Copenh). 1974; 52:740–6.
15. Ehelers N, Bramsen T, Sperling S. Applanation tonometry and central corneal thickness. Acta Ophthalmol (Copenh). 1975;53:34–43.
16. Kotecha A. What biomechanical properties of the cornea are relevant for the clinician? Surv Ophthalmol. 2007;52 Suppl 2:S109–1014.
17. Congdon NG, Broman AT, Bandeen-Roche K, et al. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol. 2006;141:495–505.
18. De Moraes CV, Hill V, Tello C, et al. Lower corneal hysteresis is associated with more rapid glaucomatous visual field progression. J Glaucoma. 2012;21:209–13.
19. Medeiros FA, Meira-Freitas D, Lisboa R, et al. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. Ophthalmology. 2013;120:1533–40.
20. Wells AP, Garway-Heath DF, Poostchi A, et al. Corneal hysteresis but not corneal thickness correlates with optic nerve surface compliance in glaucoma patients. Invest Ophthalmol Vis Sci. 2008;49:3262–8.
21. Agarwal DR, Ehrlich JR, Shimmyo M, et al. The relationship between corneal hysteresis and the magnitude of intraocular pressure reduction with topical prostaglandin therapy. Br J Ophthalmol. 2012;96: 254–7.

IOP: Target Pressures

12

Stefano Miglior and Francesca Bertuzzi

Core Messages

- It is recommended that every patient have an individualized target IOP although the concept of a target IOP is debated.
- It is recognized that the target IOP level may have to be modified over time.
- Determining a target IOP level can be complicated by the intrinsic variability of IOP measurements.
- Target IOP may be a percent reduction from baseline IOP or may be an absolute reduction.

12.1 Should I Establish a Target IOP on Every Patient?

Target intraocular pressure (IOP) is a useful clinical concept in a chronic disease requiring long-term treatment. Estimating a target pressure and recording this number in the medical record helps to remind a clinician of the initial assessment of the patient's disease. Also, it can be helpful to have a reference IOP against which to compare IOP measurements over years of follow-up, since IOP level is strongly related to the risk of developing glaucoma and to progressive glaucoma damage [1–6]. The use of a target IOP, however, does not have to be taken as mandatory in clinical practice, as the scientific evidence over the concept is not yet overwhelmingly convincing. The European Glaucoma Society guidelines define target IOP as "an estimate of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage" and suggest taking life expectancy and glaucoma stage into account when setting the target IOP (e.g., target IOP should be lower if life expectancy is long and/or if glaucoma is advanced) [7].

Summary for the Clinician

- Target IOP is defined as the IOP that minimizes the risk of glaucoma progression with minimum impact on quality of life. It is an estimate based on knowledge of multiple patient risk factors.
- Target IOP is not a definitive number, and follow-up findings may lead to its re-estimation.
- Life expectancy, glaucoma severity, and IOP at which damage occurred are

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the main factors the clinician should consider when setting a target IOP; treatment-related adverse effects, health status, and compliance should also be considered.

12.2 If I Decide to Set a Target IOP, How Should I Set It: Do I Use a Percent Reduction or Aim Toward an Absolute Number?

To date there is no evidence for determining exactly how target IOP should be calculated, and there is no evidence strongly supporting one method over another. Clinical trials generally assess damage or progression in relation to mean IOP levels recorded at baseline compared to treated levels [1–6, 8]. Therefore, mean baseline IOP is the only evidence-based IOP from which to set a target IOP. In clinical trials, baseline IOP is generally determined by averaging 3–4 measurements taken at about the same hour during the day but on different days. It is recognized that the standard measure of IOP with Goldmann applanation is intrinsically variable and that IOP undergoes circadian fluctuation.

Both an absolute IOP value [5, 8] and a percent IOP reduction [1, 4] have been used as IOP treatment goals in clinical trials. In CIGTS, an individualized absolute target IOP was set for each patient whose calculation was based on the following formula: [1-(reference IOP+ CIGTS visual field score)/100 × reference IOP], where the reference IOP was the mean of six separate IOP measurements taken in the course of two baseline visits, and visual field (VF) score was the mean of VF scores from at least two Humphrey 24–2 VFs taken during two baseline visits. Minimum lowering achieved in CIGTS was 35 %, which led to a very satisfactory outcome over time with only a small proportion of patients (10–12 %) progressing over 5 years of follow-up study [8]. The adoption of a fixed percent IOP reduction for all patients as seen in OHTS (20 % reduction goal) led to a clinically and statistically significant protective effect as well [1].

In the EMGT, a study population with early glaucoma similar to the CIGTS, no target IOP was set. Patients were randomized to either treatment with beta blocker and trabeculoplasty or observation. A relatively high proportion of patients progressed in this study; at 5 years, 44 % in the treatment arm and 66 % in the observation arm progressed, and this grew to 59 and 76 % [4], respectively, at 8 years [9].

The only study to identify a precise IOP level that helped to avoid further optic nerve damage in the entire study population was the Advanced Glaucoma Intervention Trial (AGIS) [5]. It identified 18 mmHg as a level that prevented further optic nerve damage in advanced glaucoma. Obviously, 18 mmHg will not be an appropriate target IOP for every patient, as many patients suffer glaucomatous damage without ever having a measured IOP above 18 mmHg [10]. However, the AGIS population suffered from high-pressure glaucoma with high baseline IOPs.

Using either an absolute number regardless of baseline IOP, for example, 12 mmHg or less for every advanced case of glaucoma, or a percent reduction from baseline IOP may both be suitable methods of determining target IOPs. At present, there is no strong evidence available to support one approach or the other. In fact, it seems reasonable to explain the different progression rates in CIGTS, EMGT, and OHTS on the basis of the different stages of disease enrolled in each study (glaucoma vs. ocular hypertension) and on the different, and possibly insufficient, percent IOP reductions from baseline (>35 % in CIGTS, 25 % in EMGT, 20 % in OHTS). The clinician should also bear in mind that the percent IOP reduction depends on the baseline IOP value. A target IOP reduction of 25 % will lead to different absolute IOP reduction if the baseline IOP is 24 or 12 mmHg. For example, a 25 % reduction from 24 is 18 (a 6-point decrease) and from 12 is 9 (only a 3-point decrease).

Today, it is generally accepted that each individual patient deserves an individual treatment goal, despite of lack of specific evidence for this practice. Quality of life, health status, and

adherence/persistence with medical treatment are other important factors that may influence the IOP target level estimated to be safest for a patient. Since it is impossible to know if the initially estimated target IOP will truly be safe, reassessment of the established value over time may be necessary.

Summary for the Clinician

- Target IOP can be a percent reduction from the mean baseline IOP or an absolute number depending on the stage of disease and should be individualized to the patient.
- Landmark trials generally have determined the target IOP from a mean baseline IOP that is derived from multiple IOP measurements on different days but at the same time of day.
- There is no evidence that favors one method of target IOP estimation over the other although it seems that lower target IOP is beneficial in more advanced disease.

12.3 How Should I Use Information About Diurnal IOP, Nocturnal Peaks, and Intervisit Fluctuation in Establishing a Target IOP?

Target IOP should be established of a patient's baseline IOP. However, it is difficult to truly know a patient's baseline IOP because IOP fluctuates. This fluctuation may be particularly large in certain glaucomas (chronic angle-closure, pseudoexfoliative, and pigmentary dispersion glaucoma) [11–13]. Before setting a target IOP, it is recommended that the daily range of IOP fluctuation is determined, if possible. This may require obtaining multiple IOP measurements at different times of the day. Measuring a diurnal curve may be revealing in those subjects with pronounced damage in spite of "normal" IOP measurements during office hours. However, it must be recognized that our landmark trials have not been this thorough in estimating baseline IOPs, but instead have generally used a mean of several IOP measurements taken at a similar time of day.

Several patterns of diurnal IOP variation have been described in normal and glaucomatous eyes [14]. Most individuals tend to experience higher IOP in the morning, but in some IOP peaks in the evening. The question then is: are we capturing the peak IOP that may be causing glaucomatous damage with our office measurements? At least one study suggests that office measurements reflect nocturnal peak IOP in untreated glaucoma patients [15].

12.3.1 Diurnal IOP Variation and Glaucoma

Few studies have aimed specifically to assess 24 h IOP variations in glaucoma [14–18]. In a study using self-tonometry performed at home, Asrani et al., found diurnal IOP fluctuation (defined as 5 measurements during the daytime for 5 consecutive days in 105 eyes of 64 patients) to be a significant risk factor for glaucoma progression, even after adjusting for office IOP, age, race, and VF damage at baseline [16]. These findings are interesting, but the limitations of the study must be acknowledged—criteria for VF and optic nerve progression were not specified; IOP levels during follow-up beyond the 5 days and the need for additional medications to keep IOP under 25 mmHg were not considered in the analysis; and a high number of patients were lost during the follow-up. Moreover, methods used in this study are not practically repeatable in clinical practice, and the results have not been replicated.

In a study by Bengtsson and Heijl on ocular hypertensive patients, an association between diurnal IOP fluctuation, repeatedly measured over a follow-up of at least 10 years, and conversion to POAG was not found [17]. An interesting study performed by Liu and colleagues using a sleep lab to examine IOP in healthy subjects and untreated glaucoma patients over a 24 h period did not find any significant

correlation between IOP fluctuations and glaucoma diagnosis and actually found that the extent of around the clock IOP fluctuation was larger in the normal group than in the glaucoma group [18].

12.3.2 Intervisit IOP Fluctuation and Glaucoma

As far as long-term IOP variation is concerned with glaucoma development and progression, the evidence is controversial [19]: an analysis of AGIS data performed by Nouri-Mahdavi et al. [20] found intervisit fluctuations (expressed as the standard deviation (SD) of all available IOP measurements during follow-up after initial surgical procedure) to be an independently strong risk factor for progression. Some important limitations of this study are that all IOPs were considered, including those recorded after the occurrence of VF progression (treatment could have been intensified at that time). In a subsequent analysis of the same AGIS data, Caprioli and Coleman [21] only considered IOPs up to the date of documented progression and only patients that underwent surgical procedure during follow-up, and they found that long-term fluctuation was a significant risk factor for progression only for patients in the lower mean IOP range. Neither of these reports detected a significant correlation between mean IOP and IOP fluctuation in AGIS patients.

Hong et al. examined a large number of POAG and CACG patients ($n=408$) after combined cataract extraction and trabeculectomy. A subset of patients with baseline IOP levels less than 18 mmHg was subdivided into two groups: those with small long-term fluctuations (SD of mean follow-up IOP ≤ 2 mmHg) and those with large long-term IOP fluctuations (SD of mean follow-up IOP >2 mmHg). The small fluctuation group was found to have significantly better VF outcome (mean deviation) based on Pointwise Linear Regression Analysis [22]. However, the authors did not take into account the fact that IOP variations may have been induced by escalation of medical treatment after VF changes were detected during the clinical follow-up of the patients (10 years).

Since the most significant correlations between long-term IOP fluctuation and glaucoma progression were found in eyes with lower mean IOPs in these last two studies, it is suggested that keeping a stable IOP may be more important in this subset of patients. This makes a lot of sense when one considers IOP fluctuation as a percent variation rather than as an absolute number (e.g., 2 mmHg fluctuation is 20 % of 10 mmHg and only 10 % of 20 mmHg mean IOP).

The EMGT examined long-term IOP fluctuation as a risk factor for glaucoma progression (using predefined VF criteria) in a population of 255 glaucoma patients over 8 years of follow-up. While long-term fluctuation was not correlated to VF worsening, mean IOP was confirmed as a strong risk factor for progression (mean IOP and large fluctuation, however, were correlated) [9]. Consistent with the EMGT, the EGPS [3] and the Diagnostic Innovations in Glaucoma Study (DIGS) [23] did not find long-term IOP fluctuations to be an independent risk factor for glaucoma development among patients with ocular hypertension.

The prognostic value of both short-term and long-term IOP fluctuation seems controversial. There is little evidence available today to support the need for diurnal or 24 h IOP evaluation in clinical practice. However, it appears that bigger swings in long-term IOP fluctuation seem to increase the risk for progression when the mean IOP is particularly low, whereas it does not seem to significantly affect the outcome when the mean IOP is medium to high.

Summary for the Clinician

- Both circadian and intervisit variations are usually correlated with mean IOP level.
- The prognostic value of short- and long-term IOP fluctuation is controversial.
- An overview of the debated literature supports the hypothesis that long-term fluctuation may be more harmful in eyes with lower mean IOPs.
- In clinical practice, if diurnal IOP curves cannot be assessed, it would be wise to record the time of each IOP measurement.

12.4 Are Supine and Nocturnal IOPs Important to Factor into Target Pressure Estimation?

No study to date has looked into this question, and therefore, it is difficult to directly answer whether the magnitude of increase in IOP in the supine position should be taken into account when considering a patient's baseline IOP. There is a significant difference between IOP readings taken in the sitting and supine positions [14, 15, 18], with supine IOP generally being higher. Although aqueous production decreases at night [24], the supine position assumed on going to sleep causes IOP to increase because episcleral venous pressure increases when one's head is at the same level as the heart. This has been shown to be true in both normal and glaucomatous subjects, although the phenomenon is less pronounced in older glaucomatous subjects when compared to a younger normal population [14].

From studies on 24 h assessment of IOP in sleep labs, the clinician should be aware that sitting office measurements may underestimate peak IOP values. A study concerning IOP measurement in a sleep lab with pneumatonometry examined the correlation between diurnal sitting and nocturnal supine IOPs in three groups: young healthy (18–25 years), older healthy (40–74), and older untreated glaucoma patients (40–79). In a majority of the glaucoma patients (67.2 %), the highest IOP value was measured at night, in the supine position. The strongest correlation between nocturnal peaks and diurnal sitting IOP values was found in the glaucoma group, while a weaker correlation was seen in the older healthy group and no correlation was seen in the younger healthy subjects [15]. Further investigations on larger samples are needed to confirm these findings.

A practical way to estimate the night time IOP peak might be to measure IOP in the supine position during an office visit. These daytime supine values have been reported to be highly consistent with supine IOPs recorded at night [14, 18]. Therefore, this effect seems not to be dependent on the time of the day but rather on the body position. These IOP variations may be physiologically compensated for by the perfusion changes and cerebrospinal fluid (CSF) changes that also occur in the supine position.

Another way to possibly identify patients with a tendency toward high IOP peaks is provocative testing, such as the steroid and water drinking tests [25]. These tests are somewhat unpractical and time-consuming; however, studies recently performed [26–29] have shown that the water drinking test can predict IOP peak and possibly the likelihood of progression as well as treatment response. Since this kind of test is simple and safe, its clinical employment should deserve some attention in the future.

Summary for the Clinician

- IOP is usually higher at night due to increased episcleral pressure in the supine position.
- Physiologic compensations in perfusion and CSF changes probably compensates for the increase in IOP (this is not yet fully understood).
- There are differences in supine IOPs between younger and older individuals, as well as between healthy and glaucoma patients.
- Some reports show a correlation between office IOPs and nocturnal/supine peak in glaucoma patients and suggest that the peak value might be predicted by office measurements.
- Nocturnal IOP peaks may be estimated by taking diurnal IOP measurements in the supine position.

References

1. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:710–3.
2. Higginbotham EJ, Gordon MO, Beiser JA, et al. The Ocular Hypertension Treatment Study: topical medication delays or prevents primary open-angle glau-

coma in African American individuals. Arch Ophthalmol. 2004;122:813–20.
3. Miglior S, Torri V, Zeyen T, Pfeiffer N, Vaz JC, Adamsons I, EGPS GROUP. Intercurrent factors associated with the development of open-angle glaucoma in the European Glaucoma Prevention Study. Am J Ophthalmol. 2007;144:266–75.
4. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol. 1998;126:498–505.
5. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol. 2000;130:429–40.
6. Hejil A, Leske MC, Bengtsson B, Hyman L, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268–79.
7. The European Glaucoma Society. Terminology and guide-lines for glaucoma. 2nd ed. www.eugs.org.
8. Lichter PR, Musch DC, Gillespie BW, et al. CIGTS Study Group. Interim clinical outcome in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medication or surgery. Ophthalmology. 2001;108:1943–53.
9. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z, For The Early Manifest Glaucoma Trial Group. Predictors of long-term progression in the Early Manifest Glaucoma Trial. Ophthalmology. 2007;114:1965–72.
10. Anderson DR, Drance SM, Schulzer M. Factors that predict the benefit of lowering intraocular pressure in normal tension glaucoma. Am J Ophthalmol. 2003;136:820–9.
11. Ritch R, Lowe RF. Angle-closure glaucoma: clinical types. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas. St Louis: CV Mosby; 1996. p. 829–40.
12. Altintas O, Yüksel N, Karabas VL, Qağlar Y. Diurnal intraocular pressure variation in pseudoexfoliation syndrome. Eur J Ophthalmol. 2004;14:495–500.
13. Karickoff JR. Reverse pupillary blocking pigmentary glaucoma: follow-up and new developments. Ophthalmic Surg. 1993;24:562–3.
14. Liu JH, Kripke DF, Twa MD, et al. Twenty-four hour pattern of intraocular pressure in the aging population. Invest Ophthalmol Vis Sci. 1999;40:2912–7.
15. Mosaed S, Liu JHK, Weinreb RN. Correlation between office and peak nocturnal IOP in healthy subjects and glaucoma patients. Am J Ophthalmol. 2005;139:320–4.
16. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134–42.
17. Bengtsson B, Heijl A. A long term prospective study of risk factors for glaucomatous visual field loss in patients with ocular hypertension. J Glaucoma. 2005;14:135–8.
18. Liu JHK, Zhang X, Kripke DF, Weinreb RN. 24 hour IOP pattern associated with early glaucomatous changes. Invest Ophthalmol Vis Sci. 2003;44:1586–90.
19. Palmberg P. What is it about pressure that really matters in glaucoma? Ophthalmology. 2007;114:203–4.
20. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627–35.
21. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the Advanced Glaucoma Intervention Study. Ophthalmology. 2008;115:1123–9.
22. Hong S, Hong JG, Seong GJ. Long-term intraocular pressure and visual field progression in glaucoma patients with low intraocular pressure after a triple procedure. Arch Ophthalmol. 2007;125:1010–3.
23. Medeiros FA, Weinreb RN, Zangwill LM, et al. Long-term intraocular pressure fluctuations and risk of conversion from ocular hypertension to glaucoma. Ophthalmology. 2008;115:934–40.
24. Maus TL, Mclaren JW, Shepard JWJR, Brubaker RF. The effects of sleep on circulating catecholamines and aqueous flow in human subjects. Exp Eye Res. 1996;62:351–8.
25. Spaeth GL. Effects of topical dexamethasone on intraocular pressure and the water drinking test. Arch Ophthalmol. 1966;76:772–83.
26. Brubaker RF. Targeting outflow facility in glaucoma management. Surv Ophthalmol. 2003;48 suppl 1:S17–20.
27. Susanna Jr R, Vessani RM, Sakata L, et al. The relation between intraocular pressure peak in the water drinking test and visual field progression in glaucoma. Br J Ophthalmol. 2005;89:1298–301.
28. Susanna Jr R, Medeiros FA, Vessani RM, et al. Intraocular pressure fluctuations in response to the water-drinking provocative test in patients using latanoprost versus unoprostone. J Ocul Pharmacol Ther. 2004;20:401–10.
29. Susanna Jr R, Hatanaka M, Vessani RM, et al. Correlation of asymmetric glaucomatous visual field damage and water-drinking test response. Invest Ophthalmol Vis Sci. 2006;47:641–4.

IOP: Fluctuation

13

Marla B. Sultan and Paul P. Lee

Core Messages

- Both short-term and long-term intraocular pressure (IOP) fluctuation may impact the prognosis of glaucoma and glaucoma suspects.
- The existing literature on IOP fluctuation can be interpreted in many ways; the true impact of fluctuation remains unclear.
- For every patient, treatment for glaucoma is a balance between expected risks of worsening and expected benefits of treatment.
  - Inconsistent usage of medications may increase long-term IOP fluctuation.
  - Surgery reduces both long-term and short-term fluctuation.

13.1 Why Is IOP Fluctuation a Topic of Interest?

Glaucoma is a leading cause of visual impairment and blindness in the United States [1, 2] and worldwide [3]. Lowering intraocular pressure (IOP) is the only proven means to slow or halt disease progression in those at higher risk of developing glaucoma (Ocular Hypertension Treatment Study [OHTS]) [4], in those with early to moderate glaucoma (Collaborative Initial Glaucoma Treatment Study [CIGTS] [5] and Early Manifest Glaucoma Trial [EMGT]) [6, 7], in those with more advanced glaucoma (Collaborative Initial Normal-Tension Glaucoma Study [CNTGS] [8, 9] and Advanced Glaucoma Intervention Study [AGIS]) [10]. Across all randomized, controlled trials, lowering IOP by at least 18 % (mean) from baseline results in a 40 % or greater reduction in glaucoma progression over 5 years [5–7, 9].

Past observations that glaucoma patients experience a wider range of IOP fluctuation than normal patients may indicate a greater propensity for glaucomatous worsening in eyes with greater IOP fluctuation. Indeed, several (but not all) recent publications have highlighted the likelihood of worsening glaucoma among those individuals with larger IOP swings within defined time periods [6, 10–13]. It is important to keep

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the concepts of short-term and long-term IOP fluctuation separate. For the purposes of this chapter, we use "short-term" fluctuation to represent IOP variation within a 24 h time period, while "long-term" fluctuation represents variation across different days.

Summary for the Clinician

- IOP fluctuation is a proposed risk factor for glaucoma development and progression.
- "Short-term" fluctuation represents IOP variation within a 24 h time period.
- "Long-term" fluctuation represents variation across different days.
- Different conclusions can be drawn from the literature concerning IOP fluctuation; however, there is a growing belief that larger long-term fluctuation is associated with progression of disease.

13.2 What Factors Should Be Considered When Measuring Short-Term IOP Fluctuation?

Regardless of how IOP is measured, a single in-office IOP measurement will not capture an individual eye's entire IOP range [14]. In normal individuals, IOP has been reported to fluctuate 2–6 mmHg over a 24 h period, while in an eye with glaucoma fluctuation it can be significantly greater than 6 mmHg [15]. In fact, it has been suggested that if fluctuation of 10 mmHg or more is seen within a 24 h period that glaucoma should be suspected [16]. Traditionally, peak IOP was believed to occur early in the morning, but recent research has indicated that some individuals peak in the afternoon or evening, and yet others have no reproducible pattern of IOP fluctuation [16]. In order to understand the extent of IOP change over a 24 h time period, IOP needs to be measured at various times during the day in each individual [17].

Some glaucoma specialists consider a sleep lab assessment of IOP over a 24 h time period with multiple measurements (every 2 h including the moment the patient wakes up) to be the gold standard evaluation of short-term IOP. However, virtually all agree that sleep lab assessment is impractical in the large majority of patients and has significant limitations (e.g., waking the patient, whether patient is supine or sitting).

Short-term IOP fluctuation is often assessed with office measurements, typically between 7 a.m. and 6 p.m. A few published papers include a late evening IOP measurement taken as late as midnight. However, one study [18] has noted that IOP measurement during routine office hours can miss up to 62 % of IOP peaks found in testing outside of office hours [17] and up to 88 % of IOP troughs [14, 17]. No study has specifically reported on the test–retest reliability of either sleep lab or in-office IOP measurements over a prolonged or 24 h time period.

Summary for the Clinician

- In order to understand the extent of IOP fluctuation in an individual over a 24 h time period, IOP needs to be measured at various times over the course of a day.
- IOP measurement during routine office hours can underestimate peak IOP and the range of fluctuation—it may miss up to 62 % of IOP peaks found in testing outside of office hours as well as 88 % of IOP troughs.
- A sleep laboratory may provide the most controlled setting for measuring IOP over a 24 h time period, but it has both practical and scientific limitations.

13.3 What Is the Significance of Short-Term IOP Fluctuation?

The primary question that clinicians and researchers have been asking is whether or not larger IOP fluctuations over a 24 h period confer greater risk of developing glaucoma and progressing to more advanced stages of disease. Several studies have assessed the relationship between short-term IOP fluctuation as measured in the office setting and the status of ocular hypertension and glaucoma patients [11, 13, 19–22]. Some of these studies indicate no association between short-term fluctuation and the development or progression of glaucoma. However, there are two studies that do show an association between short-term fluctuation and increased likelihood of disease. Mean short-term IOP fluctuation (measured at 2 h intervals from 10 a.m. to 6 p.m.) was found to be 8.6 mmHg in an Indian ocular hypertensive population that progressed to POAG compared to 5.4 mmHg in the group that did not progress (relative risk of 9.1 (95 % confidence interval [CI]: 2.2–163.4)) [21]. In another study, Gonzalez et al. [19] demonstrated that 64 % of ocular hypertensives with short-term IOP fluctuation greater than 5 mmHg (measured every 2 h beginning at 8 a.m. for a minimum of 12 h) developed glaucomatous visual field defects within 4 years compared to 18 % with lower fluctuation ($p < 0.05$).

In summary, there are studies on both sides of the short-term fluctuation debate. Some support the notion that greater fluctuation increases the risk of glaucoma and its rate of worsening, while others do not. In the studies that do not show a relationship, weaknesses include the fact that IOPs were not assessed at time points shown to be potentially important (i.e., nighttime IOP) [23–25] and patients were under treatment with drug classes shown to reduce fluctuation as part of their treatment profile [13]; therefore, it is difficult to say with confidence what is the true impact of short-term fluctuation.

Summary for the Clinician

- There is conflicting data regarding the effect of short-term IOP fluctuation on glaucoma development and progression.
- Some studies indicate that short-term IOP fluctuation is associated with a greater risk or rate of worsening of status among patients with both ocular hypertension and glaucoma, while others show no effect.

13.4 What Factors Should Be Considered in Measuring Long-Term IOP Fluctuation?

Because long-term IOP fluctuation requires measurement of IOP over different days and visits, sleep lab assessments evaluating multiple 24 h periods and across different days have not been published. Thus, long-term IOP fluctuation has only been assessed with measurements taken in the office setting and, in one study by Asrani et al. [26], in the home setting. Unfortunately, many questions remain unanswered in terms of long-term fluctuation including: (1) what standard deviation or amount of visit to visit fluctuation is clinically significant, (2) which is more important—fluctuation of mean IOP or fluctuation of range of IOP, and (3) what is the effect of IOP fluctuation due to inconsistent use of medications.

Summary for the Clinician

- Long-term IOP fluctuation requires measurement of IOP over different days and visits.
- Settings for long-term IOP fluctuation measurements could include the laboratory, office setting, and home setting.

13.5 What Is the Significance of Measures of Long-Term IOP Fluctuation?

Asrani et al. [26] trained patients to measure their own IOP at home using a specially designed device over a 5-day period to assess diurnal IOP fluctuation's effect on glaucoma progression. After 8 years of follow up, they found that progression occurred in 88 % of patients in the upper 25th percentile of IOP fluctuation (11.8 mmHg) and in 57 % of patients in the lower 25th percentile of IOP fluctuation (7.7 mmHg) based on the single 5-day period of IOP monitoring, and it was independent of office IOP, age, race, gender, and visual field damage at baseline [26]. The hazard ratio for glaucoma progression was 5.69 (95 % CI: 1.86–7.35; $p<0.0005$ comparing those in the upper 25 % with those in the lower 25 %).

Aside from Asrani's work, all other studies assessing IOP fluctuation and its relationship to glaucoma status used in-office measurements during routine office hours. No studies have assessed how many different office visits should be included in analyses and whether the time period for office visits should differ from visit to visit.

While EMGT confirmed that elevated IOP is a strong risk factor for glaucoma progression [6, 7, 12], with hazard ratio increasing by 11 % for every 1 mmHg of increase in IOP, long-term IOP fluctuation was found not to be an independent factor in analyses. In contrast, using an associative analysis of the percent of visits where IOP was less than 18 mmHg [10], the AGIS investigators found that patients whose IOP measurements were always under 18 mmHg, and who therefore presumably had less IOP fluctuation (mean IOP 12.3 mmHg during the first 6 years), had almost no mean worsening of visual field defect scores from baseline to follow up over 6 years. In contrast, patients with IOP measurements both above and below 18 mmHg at visits experienced a one-unit loss of visual field (roughly, on a 20-point scale) at 5 years (p-values between 0.01 and 0.06 for the three groups) and an additional two-unit loss at 7 years (p-values between 0.001 and 0.03). Mean IOP was 20.2 mmHg for those with IOP below 18 mmHg at less than 50 % of their visits, 16.9 mmHg for those with 50–74 % of their visits below 18, and 14.7 mmHg for those between 75 and 99 % of visits below 18 mmHg. In another analysis of AGIS data [27, 28], use of standard deviation as a measure of variation was shown to be of value in understanding IOP fluctuation over time. Four variables were associated with a higher probability of visual field progression as assessed by pointwise linear regression: older age at the time of first intervention ($p=0.0012$), greater IOP fluctuation, as measured by the standard deviation of IOPs from visit to visit ($p=0.0013$), increasing number of glaucoma interventions ($p=0.0103$), and longer follow-up ($p=0.0223$) [27, 28]. The possible factors that might underlie the different findings with different studies include: (1) the AGIS analyses [27, 28] included postprogression IOP values, which might be biased toward larger fluctuations induced by more intensive treatment; (2) study population differences; and (3) significant differences in the baseline IOPs of the different studies, with the EMGT population having a much lower baseline IOP. The most recent analysis of the AGIS population, which removed posttreatment IOPs, maintains that long-term fluctuation in IOP was associated with visual field progression (26 % of eyes) ($p=0.009$). However, IOP fluctuation was only found to be associated with visual field progression in the low mean IOP group ($p=0.002$) and not in the high mean IOP group ($p=0.2$).

Additional studies from other sources also tend to support the importance of long-term IOP fluctuation. Analysis of the Olmsted County data [29] indicates that a greater range of IOP from visit to visit is associated with a greater risk of progression to blindness. Similarly, studies by Bergea et al. [12] and O'Brien et al. [29] suggest that understanding the range of IOP over time may be another simple but useful means to glaucoma progression.

Summary for the Clinician

- Several studies have demonstrated conflicting results with regard to the importance of assessing long-term IOP fluctuation. Studies following IOP over longer time intervals suggest an association between greater fluctuation and glaucoma progression. Newer analyses of data now suggest that fluctuation may be more important in patients starting off with lower levels of IOP.
- Different definitions of long-term fluctuation, analyses, study populations, treatment regimens, time periods of IOP measurement and baseline IOPs make direct comparison between the various studies examining IOP fluctuation difficult.
- Additional investigation is needed to better understand the best method for assessing long-term IOP fluctuation and the value of measuring long-term IOP fluctuation.

13.6 What Is the Impact of Medication on Short-Term and Long-Term IOP Fluctuation?

Analysis of published studies suggests that prostaglandin analogs and combination beta-blockers/carbonic anhydrase inhibitors are most effective in reducing short-term IOP fluctuation [30], while topical carbonic anhydrase inhibitors alone and possibly alpha-adrenergic agonists alone are superior to beta-adrenergic blockers alone. Few studies have specifically analyzed long-term IOP fluctuation. Additional analyses that report standard deviations for IOP would be helpful to better understand the differences, if any, among the medication classes in controlling long-term IOP fluctuation.

Patients who intermittently use their medication may be exaggerating both short- and long-term IOP fluctuation in their own eyes. Unlike patients enrolled in clinical trials, patients cared for in routine clinical environments do not benefit from the supportive infrastructure of a trial that helps them obtain and use medications as directed and to follow up at regular intervals. Indeed, even for patients enrolled in clinical trials, as in AGIS [10], significant fluctuations in IOP from visit to visit (long-term IOP fluctuation) can occur; to what degree this is due to the disease versus to poor adherence with prescribed medications cannot be determined. However, intermittent usage of medications over sufficiently long periods of time may result in greater levels of IOP fluctuation and long-term IOP fluctuation.

Summary for the Clinician

- Patients who consistently take medication as prescribed presumably have lower degrees of IOP fluctuation compared to untreated patients.
- Analysis of published studies suggests that prostaglandin analogs and combination beta-blockers and carbonic anhydrase inhibitors are most effective in reducing short-term IOP fluctuation. Few studies have specifically analyzed long-term IOP fluctuation.
- Lack of adherence and persistence with medication regimens may induce significant short and long-term fluctuation.

13.7 What is the Impact of Surgery on Short-Term and Long-Term IOP Fluctuation?

It has been demonstrated that argon laser trabeculoplasty decreases mean short-term IOP fluctuation by 30 % when compared to pretrabeculoplasty IOP [31]. Other studies have confirmed this finding [32, 33]. However, such a reduction, while important in absolute numbers of mmHg, may not reflect a significant change in percent reduction relative to IOP peak or trough since these values are reduced by the treatment as well.

Several studies have addressed the question of whether IOP fluctuations are best controlled by medical therapy or incisional surgery. They have found that short-term IOP fluctuation is best controlled with surgical therapy [34–36]. Intraocular peak pressure and short-term IOP fluctuation measured following water-provocative testing were significantly greater in 30 patients with POAG using ocular hypotensive medication and no history of glaucoma-related surgery as compared to 30 such patients who had undergone one or more trabeculectomies ($p < 0.05$ for both comparisons) [35]. Similarly, a prospective observational study in 60 patients found that a well-functioning trabeculectomy provided a statistically lower mean, peak, and range of IOP over the 24 h day than the maximally tolerated medical therapy in patients with advanced glaucoma ($p \leq 0.0001$ for each comparison) [34].

In terms of long-term IOP fluctuation, filtration surgery has been shown to enhance the effect of reducing IOP changes as compared to ocular hypotensive medications [37].

Summary for the Clinician

- Several studies have addressed the question of whether IOP fluctuations are best controlled by medical therapy or incisional surgery and have found that short-term IOP fluctuation is best controlled with surgical therapy.

13.8 How Aggressive Should I Be in Eliminating Long-Term IOP Fluctuation Given the Potential Complications of Medications and Surgery?

Given conflicting study results, an international expert panel was convened to determine the degree of consensus among glaucoma specialists concerning the measurement, characterization, and potential implications of IOP and the impact of short- and long-term fluctuation [38]. Through a modified Delphi process to assess both the presence and strength of consensus, the panel agreed that adequate means of IOP measurement exist, although the frequency at which IOP should be measured is poorly defined. The need to additionally investigate the role of IOP changes in glaucoma management was highlighted by the indeterminate and nonconsensus ratings among experts about the impact of long-term and short-term IOP fluctuation.

Furthermore, while the current weight of evidence may support long-term fluctuation as an important factor to consider, it is important to remember that long-term IOP fluctuation may also be a marker for treatment success or failure. For example, in patients on medications, IOP fluctuation may indirectly show how adherent and persistent patients are to medications. In those patients that have undergone glaucoma surgery where there is increasing IOP fluctuation, the fluctuation may actually indicate that the surgery is failing.

As such, the central consideration when recommending treatment is to take into account a patient's life stage, needs, and expectations. By involving the patient in decision-making and surveying their preferences, ophthalmologists can best meet their obligations to "first do no harm."

Summary for the Clinician

- Through a modified Delphi process, a panel of experts could not come to a consensus regarding the importance of IOP fluctuation in glaucoma
- Long-term IOP fluctuation may be a marker for how adherent and persistent patients are to medications and the success of surgery.

References

1. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol. 2004;122:477–85.
2. Friedman DS, Wolfs RC, O'Colmain BJ, et al. Prevalence of open-angle glaucoma among adults in the United States. Arch Ophthalmol. 2004;122: 532–8.
3. Pizzarello L, Abiose A, Ffytche T, et al. VISION 2020: The Right to Sight: a global initiative to eliminate avoidable blindness. Arch Ophthalmol. 2004;122:615–20.
4. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701–13; discussion 829–30.
5. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108:1943–53.
6. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120:1268–79.
7. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2003;121:48–56.
8. Group CIN-TGS. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol. 1998;126:487–97.
9. Group CIN-TGS. The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Am J Ophthalmol. 1998;126:498–505.
10. AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130:429–40.
11. Bengtsson B, Heijl A. Diurnal IOP fluctuation: not an independent risk factor for glaucomatous visual field loss in high-risk ocular hypertension. Graefes Arch Clin Exp Ophthalmol. 2005;243:513–8.
12. Bergea B, Bodin L, Svedbergh B. Impact of intraocular pressure regulation on visual fields in open-angle glaucoma. Ophthalmology. 1999;106:997–1004.
13. Jonas JB, Budde WM, Stroux A, et al. Diurnal intraocular pressure profiles and progression of chronic open-angle glaucoma. Eye (Lond). 2006;21:948–51.
14. Wilensky JT, Gieser DK, Mori MT, et al. Self-tonometry to manage patients with glaucoma and apparently controlled intraocular pressure. Arch Ophthalmol. 1987;105:1072–5.
15. Drance SM. Diurnal variation of intraocular pressure in treated glaucoma. Significance in patients with chronic simple glaucoma. Arch Ophthalmol. 1963;70:302–11.
16. American Academy of Ophthalmology. Basic and clinical science course. San Francisco: American Academy of Ophthalmology; 2006.
17. Barkana Y, Anis S, Liebmann J, et al. Clinical utility of intraocular pressure monitoring outside of normal office hours in patients with glaucoma. Arch Ophthalmol. 2006;124:793–7.
18. Mosaed S, Liu JH, Weinreb RN. Correlation between office and peak nocturnal intraocular pressures in healthy subjects and glaucoma patients. Am J Ophthalmol. 2005;139:320–4.
19. Gonzalez I, Pablo LE, Pueyo M, et al. Assessment of diurnal tensional curve in early glaucoma damage. Int Ophthalmol. 1996;20:113–5.
20. Liu JH, Zhang X, Kripke DF, et al. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. Invest Ophthalmol Vis Sci. 2003;44:1586–90.
21. Thomas R, Parikh R, George R, et al. Five-year risk of progression of ocular hypertension to primary open angle glaucoma. A population-based study. Indian J Ophthalmol. 2003;51:329–33.
22. Wax MB, Camras CB, Fiscella RG, et al. Emerging perspectives in glaucoma: optimizing 24-hour control of intraocular pressure. Am J Ophthalmol. 2002;133(Suppl):S1–10.
23. Liu JH, Bouligny RP, Kripke DF, et al. Nocturnal elevation of intraocular pressure is detectable in the sitting position. Invest Ophthalmol Vis Sci. 2003;44:4439–42.
24. Liu JH, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. Invest Ophthalmol Vis Sci. 1999;40:2912–7.
25. Liu JH, Kripke DF, Weinreb RN. Comparison of the nocturnal effects of once-daily timolol and latanoprost on intraocular pressure. Am J Ophthalmol. 2004;138:389–95.
26. Asrani S, Zeimer R, Wilensky J, et al. Large diurnal fluctuations in intraocular pressure are an independent risk factor in patients with glaucoma. J Glaucoma. 2000;9:134–42.
27. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the Advanced Glaucoma Intervention Study. Ophthalmology. 2008;115: 1123–9.
28. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111:1627–35.
29. Oliver JE, Hattenhauer MG, Herman D, et al. Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. Am J Ophthalmol. 2002;133: 764–72.

30. Orzalesi N, Rossetti L, Bottoli A, et al. The effect of latanoprost, brimonidine, and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with glaucoma or ocular hypertension. Arch Ophthalmol. 2003;121:453–7.
31. Greenidge KC, Spaeth GL, Fiol-Silva Z. Effect of argon laser trabeculoplasty on the glaucomatous diurnal curve. Ophthalmology. 1983;90:800–4.
32. Agarwal HC, Sihota R, Das C, Dada T. Role of argon laser trabeculoplasty as primary and secondary therapy in open angle glaucoma in Indian patients. Br J Ophthalmol. 2002;86:733–6.
33. Heijl A, Bengtsson B. The short-term effect of laser trabeculoplasty on the glaucomatous visual field. A prospective study using computerized perimetry. Acta Ophthalmol Scand. 1984;62:705–14.
34. Konstas AG, Topouzis F, Leliopoulou O, et al. 24-hour intraocular pressure control with maximum medical therapy compared with surgery in patients with advanced open-angle glaucoma. Ophthalmology. 2006;113:761–5.e1.
35. Medeiros FA, Pinheiro A, Moura FC, et al. Intraocular pressure fluctuations in medical versus surgically treated glaucomatous patients. J Ocul Pharmacol Ther. 2002;18:489–98.
36. Shaarawy T, Flammer J, Haefliger IO. Reducing intraocular pressure: is surgery better than drugs? Eye (Lond). 2004;18:1215–24.
37. Wilensky JT, Zeimer RC, Gieser DK, et al. The effects of glaucoma filtering surgery on the variability of diurnal intraocular pressure. Trans Am Ophthalmol Soc. 1994;92:377–81; discussion 81–3.
38. Lee PP, Sultan MB, Grunden JW, Cioffi GA, IOP. Consensus Panel. Assessing the importance of IOP variables in glaucoma using a modified Delphi Process. J Glaucoma. 2010;19:281–7.

Gonioscopy: Why Do Indentation?

14

Howard Cohn and Yves Lachkar

Core Messages

- The Van Herick method of estimating peripheral anterior chamber depth does not replace gonioscopy. Plateau iris with angle-closure may be missed completely.
- Glaucoma with a quiet painless eye and reactive pupil is not always POAG.
- Only indentation gonioscopy allows one to evaluate the dynamics of relative pupillary block, distinguish appositional from synechial angle-closure, and make an informed decision whether to perform an iridotomy.
- The diagnosis of "occludable angle" is a judgment call based on evaluation of the strength of relative pupillary block and the presence of appositional or synechial closure.
- Periodic gonioscopy is essential to evaluate progressive angle narrowing.
- Plateau iris is not an all-or-nothing phenomenon. Varying degrees of plateau are commonly found and not all plateau configurations are pathologic.
- Asian eyes have more angle-closure than African or Caucasian eyes, due to anterior iris insertion and general angle crowding. Creeping angle-closure is common and pupillary block may not be as important a factor.Anterior segment UBM or OCT exams are not substitutes for gonioscopy when making a decision about iridotomy. These exams cannot distinguish appositional from synechial closure.

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14.1 Which Patients Should have Gonioscopy?

Examination of the iridocorneal angle is an essential part of a complete ophthalmic examination, but a busy practitioner will not put a goniolens on every new patient. So, which patients should be examined? Glaucoma-related reasons to do gonioscopy include: (1) identification of eyes at risk for angle-closure; (2) evaluation of the extent of known angle-closure; (3) evaluation of the angle in any eye at risk for a secondary glaucoma:

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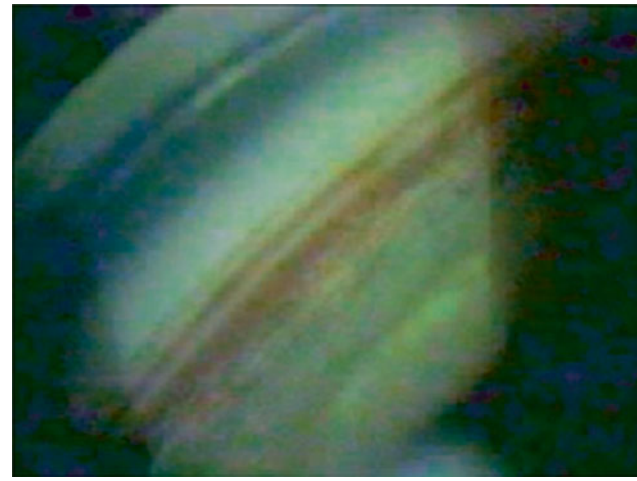

Fig. 14.1 A normal angle with wide open approach. Seen are a *brown-pigmented* ciliary body band, pigmented trabecular meshwork, and pigment on Schwalbe's line

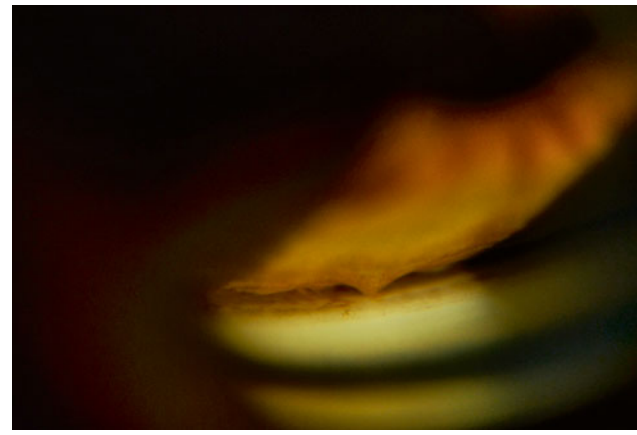

Fig. 14.2 Spot PAS to the scleral spur in an angle opened after laser peripheral iridotomy

pseudoexfoliation, pigment dispersion, uveitis, past history of contusion, retinal vein occlusion, diabetes, etc.; (4) treatment of the angle by laser: trabeculoplasty, iridoplasty, goniopuncture; (5) verification of patency of a trabeculectomy; and, last but not least, (6) learning the anatomy of the normal angle. Gonioscopy should be done routinely in cooperative patients when time permits to learn all the variations of normal angles (Figs. 14.1 and 14.2). If a lens is only put on eyes with narrow angles, it will be more difficult to distinguish normal from the pathologic.

Summary for the Clinician

- Gonioscopy should be performed
  - To learn the anatomy of the normal angle.
  - In every patient with OHT or suspect for open angle glaucoma.
  - On eyes at risk for angle-closure.
  - To evaluate the extent of known angle-closure.
  - To evaluate angles in eyes at risk for secondary glaucoma.
  - On eyes where laser or incisional angle surgery is contemplated.

To internally evaluate a trabeculectomy or tube shunt.

14.2 Of What Use Is the Van Herick Angle Examination?

The Van Herick test provides a very rapid, non-contact evaluation of peripheral angle opening [12]. A narrow slit beam is directed at the peripheral cornea just adjacent to the limbus at a 60° angle, and the distance between the endothelium and iris surface is estimated. If the anterior iris surface is very close to the endothelium (closer than ¼ corneal thickness) the angle approach is considered narrow. This examination is very useful to identify wide open angles with deep anterior chambers. A major problem with the Van Herick test is that a plateau iris configuration can be missed entirely. The angle approach may appear open despite the presence of abnormal pathology closer to the iris root. On the other hand, a fluffy, thick peripheral iris can appear as a narrow nasal or temporal angle on the Van Herick test, but gonioscopy can exhibit an open angle with no risk of angle closure. The Van Herick exam is done as a first step, but anytime there is the slightest doubt as to depth of the peripheral chamber, one must put on a goniolens.

Summary for the Clinician

- Van Herick's test evaluates the depth of the peripheral anterior chamber near the limbus.
- It is not a substitute for gonioscopy.

14.3 What Lens Should Be Used for Gonioscopy?

Standard single or triple mirror Goldmann type lenses are insufficient to evaluate the iridocorneal angle since they provide a static picture of the angle, which will not properly represent angle dynamics. Peripheral iris configuration, the amount of relative pupillary block, and the antero-posterior position of the iris-lens diaphragm vary with accommodation and pupillary diameter. Use of indentation gonioscopy is indispensable to evaluate relative pupillary block and to distinguish between appositional (reversible) and synechial (permanent) angle closure.

The classic Goldmann triple mirror lens has a contact surface diameter equivalent to that of the cornea with a small radius of curvature requiring viscous coupling fluid between it and the eye. It is impossible to indent the cornea with this lens since force is transmitted to the limbus. Instead, what is desired is for force to be transmitted across the cornea so that aqueous humor is pushed from the center of the anterior chamber into the angle. Indentation gonioscopy lenses have corneal contact surfaces 8 mm in diameter with rounded edges and a curvature close to the cornea's. See Fig. 14.3. Available lens models for indentation gonioscopy include the Zeiss glass four mirror lens on an Unger fork, Posner four-mirror lens on fixed handle, and Sussman lens without a handle.

Summary for the Clinician

- Goldmann type lenses provide a clear view of the angle but do not allow for dynamic/indentation gonioscopy
- Lenses for indentation gonioscopy should have a diameter less than the corneal diameter, which allows indentation and the forceful movement of aqueous humor into the angle under observation. They also should have a curvature equal to that of the cornea, thus avoiding the need for a viscous coupling agent.
- The Zeiss, Posner, and Sussman lenses can be used for indentation gonioscopy.
- Indentation gonioscopy is critical as it allows one to distinguish between permanent and reversible angle-closure.

14.4 How Do I Perform Indentation Gonioscopy?

One begins with a drop of topical anesthetic. If the IOP is to be measured, it is best done before gonioscopy. In a dimly lit or dark room with a fine slit beam outside of the pupil to prevent miosis, the lens is placed on the eye so that the mirrors sit in either a square or diamond configuration. No viscous fluid is required with the lenses for indentation gonioscopy. The hand holding the lens can be steadied by one finger touching the patient's cheek. Since all four mirrors have the same angle of inclination, there is no need to rotate the lens to see all quadrants. A static view is obtained first with the lens gently placed on the cornea. Then, one begins to indent.

Instead of pushing the entire lens uniformly into the cornea, we have found it best to push or "heel in" only the mirror in which you are looking (Figs. 14.4 and 14.5). Aqueous humor is pushed across the anterior chamber applying force to the peripheral iris, which will move posteriorly. A very slight movement of the lens towards the angle you are examining is also required while heeling in the mirror. You can release and reapply pressure to judge the importance of relative pupillary block (Figs. 14.6 and 14.7) or to see if appositional or synechial closure is present. The eye diagrammed in Figs. 14.4 and 14.5 would show a completely closed angle with static gonioscopy. Indentation revealed that the inferior angle in Fig. 14.4 could be opened,

Fig. 14.3 Standard triple mirror lens with large contact surface and sharp rim compared to an indentation goniolens with smaller contact surface and rounded edges

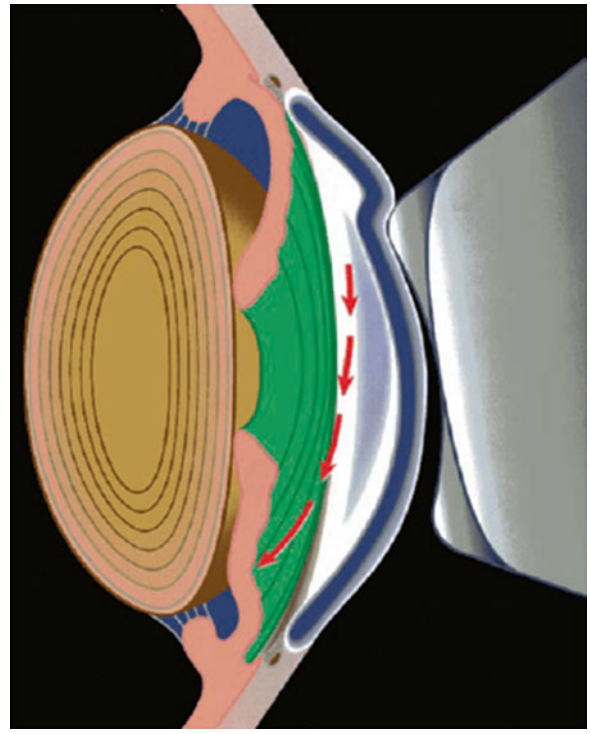

Fig. 14.4 Indenting the superior mirror moves aqueous humor across the anterior chamber forcing the peripheral iris of the inferior angle backwards. What was simply a closed angle on static gonioscopy can now correctly be identified as closed by apposition only

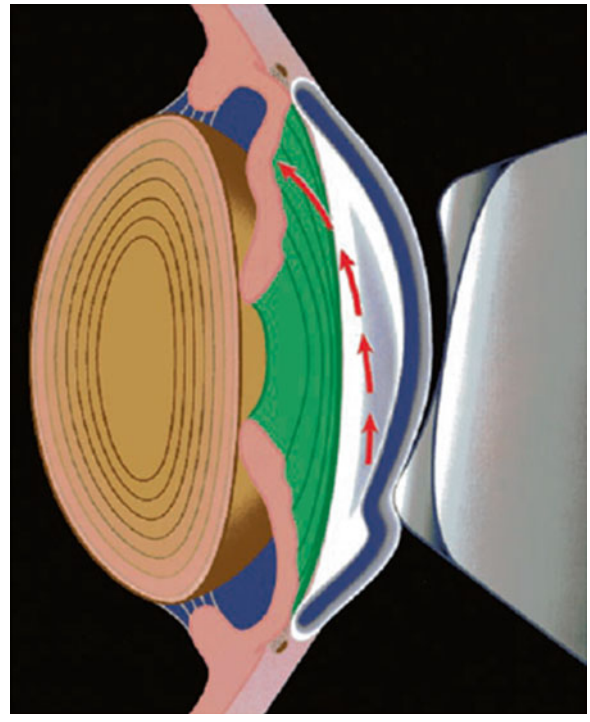

Fig. 14.5 Indentation of the inferior mirror demonstrates irreversible synechial closure of the superior angle

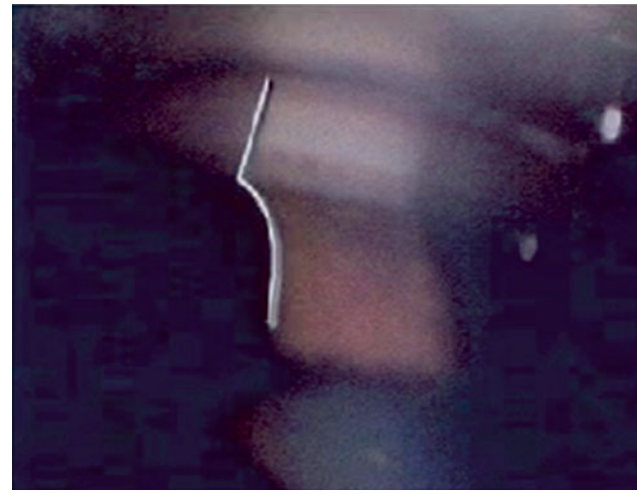

Fig. 14.6 Relative pupillary block is the phenomenon of anterior bowing of the peripheral iris due to impeded flow of aqueous humor from the posterior chamber to the anterior chamber. The static view shows the convex profile of relative pupillary block. Angle structures are still easily visible and there is no risk of angle-closure

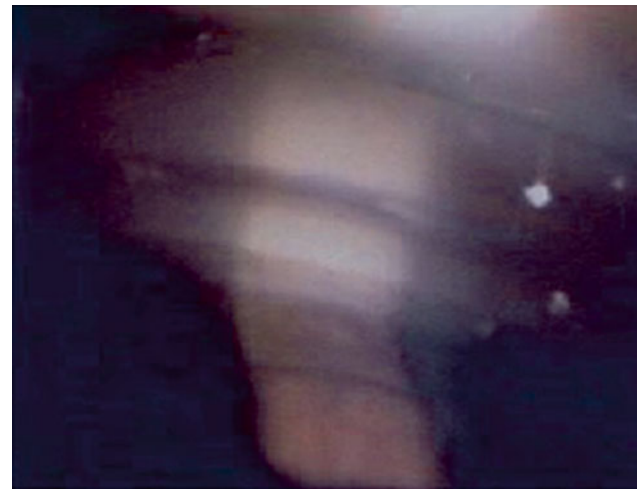

Fig. 14.7 Indentation gonioscopy can flatten out the peripheral iris. The strength of the relative block can be estimated by answering the question: how much pressure on the cornea is necessary with each indentation to move the iris backwards?

meaning there was appositional closure only. In Fig. 14.5, the superior angle remains closed by peripheral anterior synechiae (PAS). Figure 14.8a (static view) and Fig. 14.8b (during indentation) show an angle closed by apposition only. There is a definite learning curve to become comfortable with an indentation lens, but once the technique is mastered this will most likely become the only lens you use for diagnostic gonioscopy.

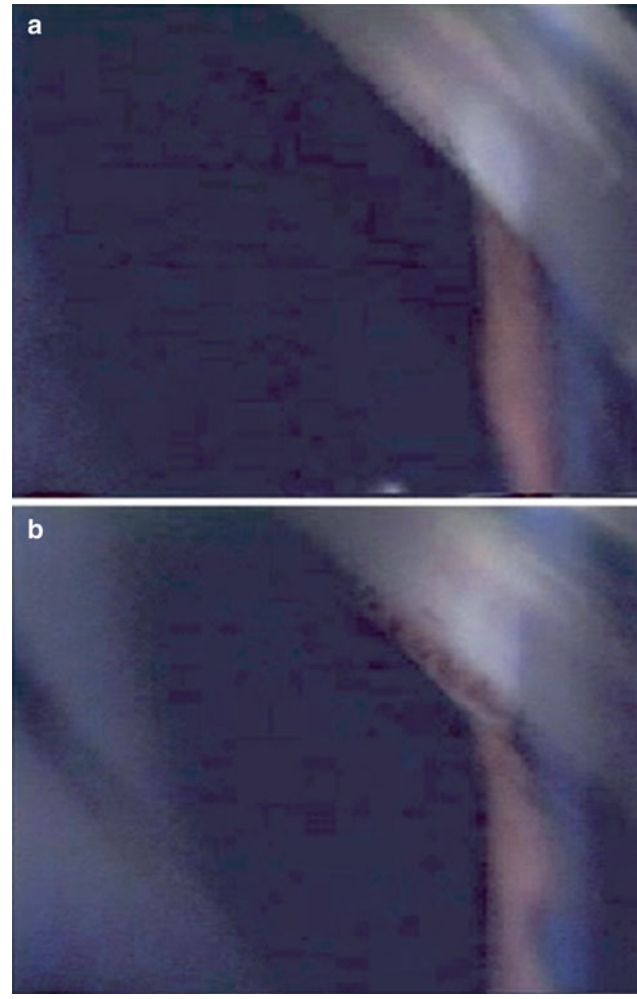

Fig. 14.8 (**a**) Static view of a closed angle. No angle elements are visible. (**b**) With indentation the angle can be opened to the scleral spur. Prolonged iridotrabecular contact can leave traces of adherent pigment seen here across the trabecular meshwork

Summary for the Clinician

- The recommended technique is to indent or "heel in" only the mirror in which the angle is being examined.
- There is a learning curve to master indentation that is well worth the effort.
- The diagnosis of "occludable angle" is a judgment call based on evaluation of the strength of relative pupillary block, and the presence of appositional or synechial closure.
- Periodic gonioscopy is essential to evaluate progressive angle narrowing.

14.5 What Should I Look for in the Angle?

Having a set routine is essential to remember what you saw when you make your notes. The peripheral iris is examined first: Is it bowed anteriorly (indicating relative pupillary block) or posteriorly (indicating reverse pupillary block)? It is important to note the strength of relative pupillary block, through resistance to indentation, since this is the element you treat with an iridotomy. Does the iris tissue look thin or thick? Note the iris color. Is there a prominent peripheral iris roll?

Next, one makes an estimation of the angle approach in degrees. The superior angle is

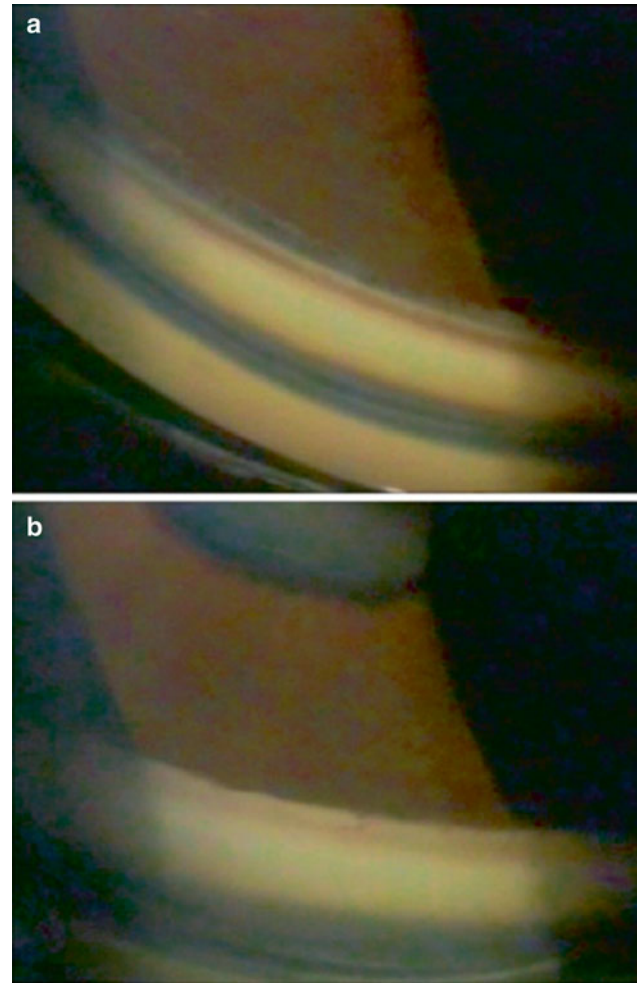

Fig. 14.9 (**a**) Traumatic angle recession in the superior angle with the ciliary body band visible and the trabecular meshwork moderately pigmented. The diagnosis was made by comparison with the normal superior angle of the fellow eye seen in (**b**)

usually narrower than the inferior angle. One notes the type of iris insertion (regular, steep, or bowed backwards), the presence of a plateau, and at what level the iris inserts (ciliary body, scleral spur, trabecular meshwork). Depending on how far the insertion is behind the scleral spur, a ciliary body band of variable depth will be present. Corresponding quadrants of both eyes should be compared to identify an angle recession, for example. (Fig. 14.9a, b) Coloration of the ciliary body band can vary from light grey to dark brown. The scleral spur may appear white or yellow or nondescript.

Iris processes, either plastered across the surface of the angle or bridging from the peripheral iris to the angle structures (Fig. 14.10) tend to be more prominent in the inferior and nasal angle. Uveal meshwork may be more or less prominent.

Angle pigmentation may or may not be limited to the trabecular meshwork. Heavy, regular, powder-like pigmentation is found in pigment dispersion syndrome. A more clumpy type of pigmentation can be found with pseudoexfoliation. Pigmentation at the level of Schwalbe's line, known as Sampoelesi's line, may be a normal variant. In an eye with nonpigmented trabecular meshwork, the ciliary body band may be mistaken for the trabecular meshwork and a false diagnosis of angle-closure can be made. The corneal wedge technique

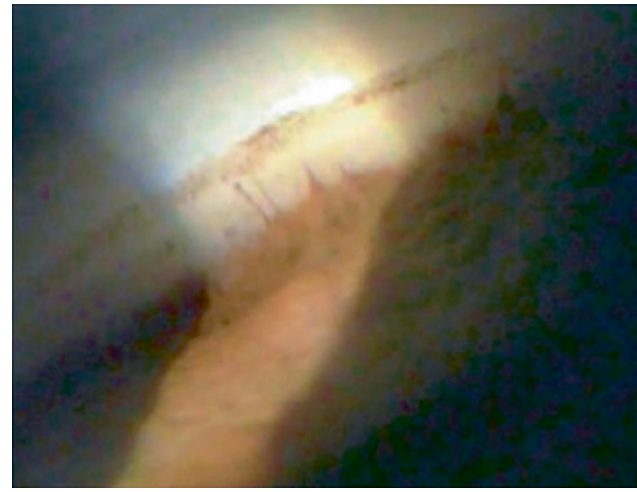

Fig. 14.10 Iris processes bridging over to the trabecular meshwork region should not be confused with PAS

Fig. 14.11 Corneal wedge showing the sharp transition from clear cornea to sclera that marks the level of Schwalbe's line. This angle without trabecular pigmentation is correctly identified as being wide open

is useful to identify Schwalbe's line and permits one to get oriented [1] (Fig. 14.11).

If peripheral iris covers the angle structures, one notes what quadrants have appositional closure and where there are PAS. Not only the location of PAS but the level to which they reach should be noted.

Depending on iris root thickness and level of insertion, there may be normal blood vessels visible that are part of the greater arterial circle of the iris. These tend to be circumferential and do not extend anterior to the scleral spur. Any vessel that crosses the scleral spur radially is likely to be pathologic, such as those found early in neovascular glaucoma.

There are different angle grading systems. The *Shaffer method* [9] of noting angle opening gives a grade 4 to an angle approach estimated at about 40°, 3 = 30°, 2 = 20°, 1 = 10°, then slit and closed. An angle between the iris and the trabecular meshwork of 20° or greater is not considered at risk for closure.

The grading system is very useful to rapidly give an idea of how narrow a given angle is, but it

does not give sufficient information to make the recommendation for a peripheral iridotomy. The *Spaeth system* [11] includes angle width (in degrees), the level of iris insertion (A–E where each letter represents a different angle structure), and iris configuration.

If the iris inserts:
anterior to Schwalbe's line = A
anterior to the posterior limit of the trabecular meshwork = B
posterior to the scleral spur = C
into the ciliary body face = D
extremely deep = E

Peripheral iris configuration (steep, regular, or queer) is partly dependent on the amount of relative pupillary block.

- "r" for regular or flat, "s" for a steep curvature or iris bombé, and "q" for a queer or concave curvature. However, the "s" configuration does not separate the steep smoothly bowing iris from one that is steep in the angle and more flat centrally (plateau iris). A "p" could be added to the classification system for this entity. The classification was modified as
- "f" for flat
- "c" for concave
- "b" for « bowed iris »
- "p" for « plateau »

Spaeth also grades posterior pigmented meshwork in the 12 o'clock angle on a scale from 0 to 4 +.

The *Scheie system* [10] is based on the most posterior visible structure in the angle on gonioscopy. Larger numbers signify a narrower angle (I: slightly narrowed angle, IV: no angle structures visible). According to Scheie, a person with grade III and IV angles are at greatest risk of angle-closure glaucoma.

The numbering of the Scheie and Shaffer systems is opposite to each other. The Shaffer system indicates the degree to which the angle is open (rather than the degree to which it is closed). To avoid confusion, must practitioners have adopted the more intuitive Shaffer system, saying a grade 4 angle is wide open.

Summary for the Clinician

- Develop a systematic routine of evaluating the angle.
- Examine the peripheral iris.
- Judge the angle approach in degrees.
- Note appearance of iris processes.
- Note degree of angle pigmentation and location.
- Look for appositional closure and PAS with indentation gonioscopy.
- Look for normal and abnormal blood vessels.
- Various grading schemes can be useful (Scheie, Shaffer, Spaeth).

14.6 How Can I Recognize Peripheral Anterior Synechiae?

PAS are abnormal adherences of the peripheral iris to the angle structures that, if extensive enough, can eventually reduce trabecular outflow. They can result from prolonged iris to angle contact in cases of pupillary block with appositional closure, intraocular inflammation, high energy argon laser trabeculoplasty, or angle neovascularization. It is important to know that PAS may begin posteriorly and can cover only the scleral spur early on. Isolated spot PAS can be confused with iris processes (Fig. 14.10) or clumped uveal meshwork. Broad PAS tend to develop with long-standing disease.

14.7 How Narrow Is too Narrow? What Are the Indications for Laser Iridotomy in a Patient with No Symptoms of Angle-closure?

The following case is illustrative: Mr. B, a 43-year-old Caucasian came for his first visit to an ophthalmologist. He saw 20/20 OU without correction and required + 1.50 D OU to read J1+.

Slit lamp examination by the Van Herick method was unremarkable except for a slightly narrow peripheral chamber depth (one-fourth corneal thickness). IOP was 18 mmHg OU with CCTs of 550 μ OU. Indentation gonioscopy of both eyes was similar: there was a moderate amount of relative pupillary block. Angle opening was estimated at 20° inferiorly and less than 10° superiorly. The iris insertion was curved to insert just behind the scleral spur with the peripheral iris not producing appositional closure in the superior angle. There was no plateau iris. The trabecular meshwork was uniformly lightly pigmented. There were no PAS. The rest of the examination was unremarkable. The assessment was that his angles were not occludable at that time. The potential problem of angle closure was discussed with a detailed explanation of the mechanism and symptoms of angle-closure. Mr. B. asked questions and apparently understood his diagnosis. He left with instructions to return in 6 months for repeat gonioscopy.

Mr. B. next came back 8 years later complaining of decreased distance and near vision. He had latent hyperopia that had become manifest requiring +1.75 D OU to see 20/20 and a +2.00 add to see J1 +. IOP was 25 mmHg O.D. and 20 mmHg O.S. Gonioscopy of the right eye showed tight appositional closure for a third of the angle superiorly and near (questionable) apposition inferiorly. No PAS were present. Post indentation gonioscopy IOP of the right eye was 16 mmHg. The angle of the left eye was slightly more open, but with questionable appositional closure superiorly. Post indentation IOP was 17 mmHg. Disk examination was unchanged. He was still totally asymptomatic.

In view of the new findings, his angles were considered occludable and a laser peripheral iridotomy (LPI) was recommended for both eyes beginning with the right eye as well as performing baseline optic disk and visual field examinations. If Mr. B. had returned sooner, the pressure rise and beginnings of angle-closure may have been evident earlier, but it is difficult to say when. In one study of 129 asymptomatic angle-closure suspects followed for 3–7 years, 25 developed angle-closure but only 8 of the 25 had any symptoms [13]. The important clinical pearl here is that these patients need to be followed with periodic gonioscopy. If the eye is judged non-occludable but suspiciously narrow, 6 months till the next checkup appears to be a reasonable interval.

The judgment of whether an angle is occludable or not depends on several findings: What structures are visible without indentation? How strong is the relative pupillary block (how much do you have to indent to flatten the peripheral iris)? Is there definite apposition and over what extent of the angle? A sign of longstanding apposition is clumpy irregular pigment deposits at the zone of iridotrabecular contact not found elsewhere in the angle. One definite indication for an LPI is the presence of even one PAS and significant relative pupillary block.

Indentation gonioscopy can provide an idea of how well an eye will do after iridotomy. If appositional closure alone is present and the IOP is not elevated, chances are good that the LPI will open the angle and stabilize the IOP. Another positive indicator is a significant drop in IOP post indentation, meaning that trabecular outflow is still functional (poor man's tonography). In eyes with chronic angle-closure, one tries to estimate how much of the angle is closed by PAS. Here again checking the IOP post indentation is important. If 75 % of the angle is permanently closed by PAS and the IOP changes little post indentation, the chances that an LPI alone will successfully control IOP are slim.

Summary for the Clinician

- Many patients with critically narrow angles may not experience classic symptoms of intermittent angle-closure.
- LPI is indicated in those patients who experience classic symptoms of intermittent angle-closure or those with PAS or significant relative pupillary block, which is judged by how much one needs to indent on gonioscopy to flatten the peripheral iris.
- In non-occludable but suspiciously narrow angles, gonioscopy performed at

6-month intervals appears reasonable to pick up progressive change.

- In an eye with chronic angle-closure and elevated IOP, a drop in IOP after indentation gonioscopy can be a good indicator of eventual success of an iridotomy.
- In angles where significant PAS have developed already, an LPI is unlikely to control elevated IOP and continued PAS formation.

14.8 What Should I Know About Plateau Iris?

Plateau iris refers to a relatively flat peripheral iris that ends with a steeper insertion of the iris root (Fig. 14.12). In the full plateau iris syndrome, angle-closure may be present, but the angle approach may appear open by Van Herick estimation with a deep central anterior chamber. The plateau configuration is due to anterior placement of the ciliary processes. It is not an all-or-nothing phenomenon. Varying degrees of plateau may be found and not all plateau configurations are pathologic. A mild plateau may rise to only the level of the scleral spur and never threaten the trabecular meshwork. Indentation gonioscopy allows one to appreciate the presence of anteriorly rotated ciliary processes through the iris, which will appear as a row of bumps or a ridge just adjacent to the iris root (Fig. 14.12a, b). This is easier to see in a lightly colored and thin iris.

The problem is that relative pupillary block and plateau iris are often found together in varying proportions (Fig. 14.13a, b). Indentation can test the strength of the relative pupillary block, identify the plateau, and see how difficult it is to open the angle. When treatment is needed, one often begins with an LPI to remove any element of pupillary block. If the angle still appears appositional with elevated pressures, argon laser iridoplasty can be performed to flatten the plateau and pull iris out of the angle [7] (Fig. 14.12b).

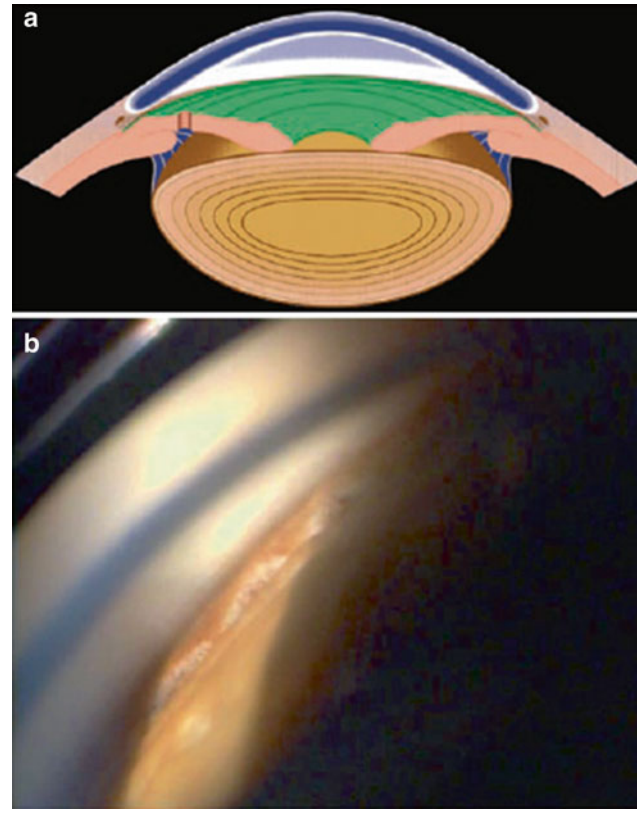

Fig. 14.12 (**a**) Pure plateau iris after removal of pupillary block by iridotomy. The iris insertion is still close to the trabecular meshwork due to anterior placement of the ciliary processes. (**b**) Plateau iris after argon laser peripheral iridoplasty. The nonperforating burns retracted the peripheral iris away from the angle structures

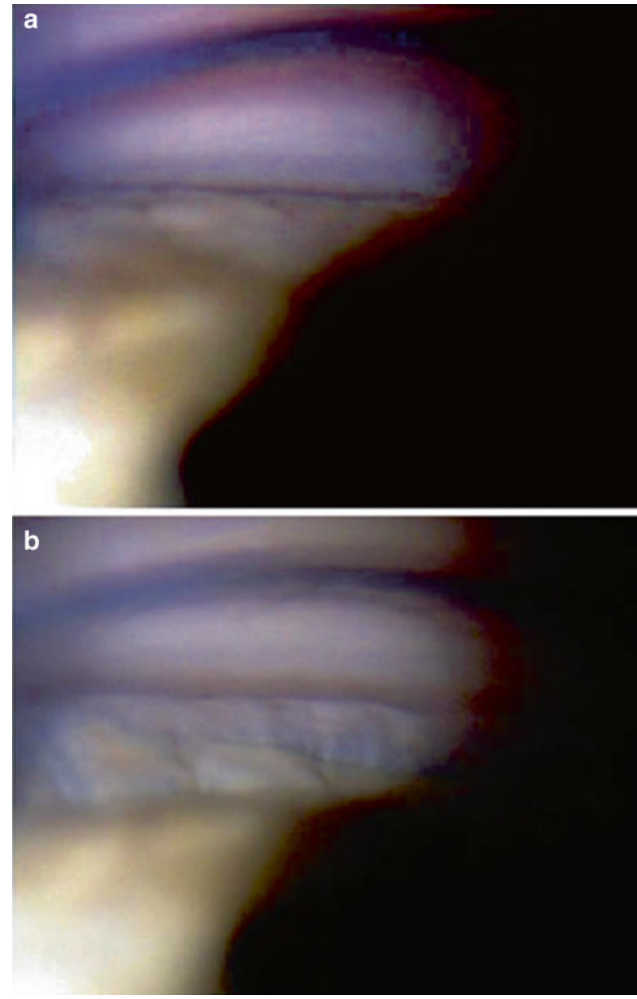

Fig. 14.13 (**a**) Pathologic plateau iris with relative pupillary block and closed angle. (**b**) Indentation of the eye reveals the closure to be appositional, and gives another illustration of the hump of anteriorly placed ciliary processes

Summary for the Clinician

- There are varying degrees of plateau iris.
- Relative pupillary block and plateau iris can be found together.
- An LPI is often used in plateau iris to remove any component of relative pupillary block.
- Argon laser iridoplasty has been used to treat plateau iris.

14.9 What Racial Differences Exist in Angle Anatomy?

Definite differences in angle anatomy have been demonstrated among racial groups. The iris insertion is most posterior in Caucasians, more anterior in Afro–Americans, and most anterior in Far East Asians. The incidence of angle-closure is correlated in the three groups, with Asians having the highest incidence of angle-closure by far [6]. Eskimos present an extreme situation. The highest incidence of angle-closure glaucoma in the

world occurs among Alaskan Eskimos and the Greenland Inuit. Eskimos tend to have shallower anterior chamber depths than other racial groups, associated with hyperopia and shorter axial lengths [14].

East Asian eyes tend to have what is called "creeping angle-closure" without the symptoms of an acute angle closure attack. This scenario may be due to anatomical differences. The ciliary body may be more anterior in Asians [5]. Pupillary block may not be as important a factor in angle-closure among Asian eyes, as evidenced by the fact that persistent angle-closure following iridotomy has been found in as much as one-fifth of treated eyes in the Liwan eye study [4]. Gonioscopy in Asian eyes can be very difficult due to the relative crowding of the anterior chamber angle with a thickly textured brown iris. A study from South Africa showed similar rates of angle-closure glaucoma among whites and blacks, but three times the rate among patients with mixed Asian origin [8]. An interesting gonioscopy finding in black Africans is that trabecular meshwork pigmentation is generally lighter than one would expect with dark skin pigmentation.

Summary for the Clinician

- Angle anatomy is different among different groups of people and the prevalence of angle closure is the highest in Asians.
- Gonioscopy may be more difficult in Asian eyes due to the relative crowding of the angle.
- In Asian eyes, pupillary block may not be the most important factor in angle-closure.

14.10 Can Anterior Segment Imaging by Ultrasound Biomicroscopy (UBM) or Anterior Segment OCT Replace Gonioscopy?

A dynamic picture of the iridocorneal angle is extremely important in deciding whether or not an iridotomy is indicated. Only indentation gonioscopy provides real-time dynamics. Sophisticated modern imaging such as UBM and anterior segment OCT, do not provide this information. These instruments can show differences in angle morphology when illumination is turned on or off, which changes the pupil size, but they cannot differentiate nearly closed from appositional closure or distinguish apposition from PAS. Both instruments are very useful to demonstrate to patients what are angle-closure and plateau iris. Anterior segment OCT gives a rapid noncontact analysis of the angle configuration. The UBM is very useful to identify information posterior to the iris such as iris and ciliary body cysts or tumors as well. As useful as the UBM and OCT are, they cannot provide the information needed to recommend an iridotomy.

Central anterior chamber depth can be measured by ultrasound, optical pachymetry, and anterior segment OCT. Shallower anterior chambers tend to have more angle-closure. As a screening tool, optical pachymetry measurement of anterior chamber depth has been found to have good sensitivity and specificity in diagnosing angle closure in Mongolia. Also, no PAS were found with anterior chamber depth greater than 2.4 mm [3]. However in an ophthalmic office practice, with careful slit lamp examination and gonioscopy, it is rare that precise measurement of central anterior chamber depth is clinically useful.

An excellent way to study the iridocorneal angle is video gonioscopy. The reader is referred to Dr. Lee Alward's internet site [2].

Summary for the Clinician

- UBM and AS-OCT are useful complements to gonioscopy.
- The change in angle configuration that is seen in a light versus dark room can be easily appreciated on UBM and AS-OCT.
- UBM and AS-OCT are not replacements for gonioscopy, which can more easily distinguish PAS from appositional angle-closure.

14.11 Indentation Gonioscopy: I don't Know What I am Seeing

Indentation gonioscopy is challenging to master, but makes your life much easier once you do so. There is a definite learning curve. You should begin with wide-open angles in cooperative relaxed patients. Normal anatomical variations will be easily learned. And, common errors will be avoided, like confusing iris processes with PAS.

Under slit lamp visualization, the inferior eyelid is retracted and the lens is gently placed directly on the center of the cornea. Only gentle contact is needed to avoid excessive pressure with inadvertent distortion of angle structures. The first thing to look for is the peripheral iris configuration, then whether you can identify Schwalbe's line, then examine the angle structures, in this order.

If you don't understand what you are seeing in one quadrant, look elsewhere to get your bearings. Indentation can be done repeatedly during one visit and at successive visits. Sometimes, it is a subsequent exam that allows you to more accurately interpret a difficult angle as the patient may be more relaxed on a return visit.

Summary for the clinician

- Perform gonioscopy in as many patients as you can to learn the normal angle variations.
- Repeat indentation with your attention first focused on the iris configuration and dynamics; and, then on the angle structures.

Acknowledgements With grateful appreciation to friend and mentor, Vicente Jocson, M.D. for teaching gonioscopy. Anterior segment drawings by Miss Annaick Peron.

References

1. Alward WLM. Color atlas of gonioscopy. London: Mosby-Year Book Europe; 1994. p. 31–4.
2. Alward WLM. Video atlas of gonioscopy. 2008. http://gonioscopy.org
3. Aung T, Nolan WP, Machin D, et al. Anterior chamber depth and the risk of primary angle-closure in 2 East Asian populations. Arch Ophthalmol. 2005;123:527–32.
4. He M, Friedman DS, Ge J, et al. Laser peripheral iridotomy in primary angle-closure suspects: biometric and gonioscopic outcomes: the Liwan Eye Study. Ophthalmology. 2007;114(3):494–500.
5. Ningli W, Wenbin Z, Tiancai Y, et al. Studies of primary angle-closure glaucoma in China. Yan Ke Xue Bao. 1997;13(3):120–4.
6. Oh YG, Minelli S, Spaeth GL, et al. The anterior chamber angle is different in different racial groups: a gonioscopic study. Eye (Lond). 1994;8(1):104–8.
7. Ritch R, Tham CC, Lam DS. Long-term success of argon laser peripheral iridoplasty in the management of plateau iris syndrome. Ophthalmology. 2004;111(1):104–8.
8. Salmon JF, Martell R. The role of ethnicity in primary angle-closure glaucoma. S Afr Med J. 1994; 84(9):623–6.
9. Shaffer RN. Primary glaucomas. Gonioscopy, ophthalmoscopy, and perimetry. Trans Am Acad Ophthalmol Otolaryngol. 1960;64:112–25.
10. Scheie HG. Width and pigmentation of the angle of the anterior chamber. Arch Ophthalmol. 1957;58:510–2.

11. Spaeth GL. The normal development of the human anterior chamber angle: a new system of grading. Trans Ophthalmol Soc UK. 1971;91:709–39.
12. Van Herick W, Shaffer RN, et al. Estimation of width of anterior chamber. Incidence and significance of the narrow angle. Am J Ophthalmol. 1969;68: 626–9.
13. Wilensky JT, Kaufman PL, Frohlichstein D, et al. Follow-up of angle-closure glaucoma suspects. Am J Ophthalmol. 1993;115(3):338–46.
14. Wojciechowski R, Congdon N, Anninger W, et al. Age, gender, biometry, refractive error, and the anterior chamber angle among Alaskan Eskimos. Ophthalmology. 2003;110(2):365–75.

Visual Fields: Visual Field Test Strategies

15

Chris A. Johnson

Core Messages

- Standard Automated Perimetry (SAP) using an adaptive forecasting threshold strategy for the central visual field remains the preferred visual field testing method for glaucoma.
- Most glaucoma clinics use adaptive forecasting threshold test procedures (SITA, ZEST, TOP, GATE) as methods for visual field testing, while FDT testing can provide a rapid, accurate, and reliable testing method for general ophthalmic practices.
- Specialized testing (SWAP, FDT, Rarebit, mfVEP, motion, flicker) may improve the ability to detect and monitor glaucomatous visual field loss in equivocal or borderline cases.
- Options exist for visual field testing of inattentive and uncooperative patients.

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15.1 What Are the Basic Differences Between Different Visual Field Machines and Tests?

15.1.1 Automated Vs. Manual

The question can be answered in many ways. First of all, there are visual field devices used to perform automated static perimetry and those for manual kinetic perimetry. *Automated* tests utilize computer programs to vary test speed, target size, and luminance. Automated tests also benefit from standardized testing conditions, which can be used to interpret results across machines, and efficient testing strategies (more on these later). They present light stimuli of varying luminance to the patient in specific locations for a given duration of time before the next stimulus is presented (0 dB is a maximal stimulus intensity, 10 dB is 1-log unit lower than the maximum, 20 dB is 2 log-units lower, etc.). Automated devices provide results that can be directly compared to age-adjusted normative values, which have been derived from testing hundreds of normal subjects. Commonly used automated perimeters are the Humphrey visual field analyzer (HFA) (Zeiss, Inc., Dublin, CA) and the Octopus perimeter (Interzeag/Haag Streit, Koeniz, Switzerland). *Manual* perimeters require a skilled examiner to present targets to the patient. Both static and kinetic testing can be performed manu-

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ally. In kinetic testing, a moving target of varying size and luminance is presented to the patient. Manual kinetic perimetry is more flexible and interactive for the patient, and it provides the opportunity to evaluate the far peripheral visual field [1]. Also in existence is a semi-automated kinetic perimetry program on the Octopus perimeter in which a computer program performs kinetic perimetry.

15.1.2 Threshold Vs. Forecasting/ Adaptive Strategies

The main differences among automated devices are related to the specific attributes of their threshold estimation strategies and test location patterns. Threshold testing quantifies visual sensitivity and involves determining the dimmest stimulus (the threshold) that can be seen at a number of predetermined test locations. Traditional threshold testing uses a staircase bracketing procedure in which stimuli of increasing intensity are projected at a test location until it is detected and then stimuli of decreasing intensity are projected until the patient fails to respond. Newer test strategies use forecasting or adaptive strategies. These strategies are able to provide threshold estimations that are similar to staircase procedures but are performed in a fraction of the time [2–4]. They include the Swedish interactive threshold algorithm (SITA), zippy estimation by sequential testing (ZEST), tendency-oriented perimetry (TOP), and the German adaptive threshold estimation (GATE).

15.1.3 Program Tests: Humphrey Field Analyzer vs. Octopus

Test procedures to evaluate the macular region, the central 30° radius, and the far peripheral visual field beyond 30° are available [1]. Each brand of machine has different names for these programs. A variety of target sizes, durations, and test presentation patterns can be selected [1]. On the HFA, the 30-2 program tests 76 points over the central 30° radius with an equidistant grid of points located 6° apart. The 24-2 program has 54 test points covering the central 24° radius, except nasally where it extends to 30°. The size III stimulus is most commonly used with these two programs. The 10-2 program has a pattern of 68 points 2° apart in the central 10° field. (The –2 refers to a Humphrey protocol in which points are tested *on either side* of the vertical and horizontal axes as opposed to *on* these axes, which would be a –1 test).

The Octopus glaucoma examination programs are called G1 and G2. They both test a 30° radius field with 59 test locations, while G2 additionally tests 14 points from 30 to 60°, and in the macular region the resolution is greater at 2.8°. Octopus program 32 tests 76 locations in an equidistant grid with 6° spacing between locations, similar to the Humphrey 30-2 program. Program C08 is similar to the 10-2 HFA program and covers the central 10° with a total of 56 test points located 2° apart [5].

15.1.4 Testing of Different Mechanisms of the Visual System

Standard automated perimetry (SAP), or white-on-white testing, is most widely used for assessing and monitoring visual field loss in glaucoma. It uses a dim white light stimulus on a dim white light background. Specific mechanisms of the visual system that are damaged in glaucoma can be evaluated with other tests. These other tests attempt to identify glaucomatous damage earlier in the process than does SAP. Isolation of short wavelength (blue cone pathway) function utilizing a yellow background and a short wavelength (blue) size V stimulus is performed with short wavelength automated perimetry (SWAP) [6, 7]. Spatial visual field properties are tested with high pass resolution perimetry (HPRP) and rarebit perimetry (RBP) [8, 9]. Temporal properties are tested with flicker perimetry, edge perimetry, flicker-defined form perimetry, and motion perimetry [10–12]. Spatiotemporal properties can be tested with frequency doubling technology (FDT) perimetry and FDT Matrix [13, 14].

Summary for the Clinician

- Many options exist today for testing visual field function/sensitivity.
- Automated visual field tests are more commonly used but kinetic tests can provide useful information in certain patients.
- Threshold estimation strategies include the time-consuming staircase bracketing strategy and newer strategies (SITA, ZEST, TOP, GATE) that mathematically predict the sensitivity of adjacent points to shorten the test.
- Test grids come in different geometric patterns with a different number of tested points located either equidistantly or at varying distances from each other.
- Newer visual field tests isolate different cell types and visual functions, including color, spatial, and temporal properties of the visual system.

15.2 What Are the Theoretical Advantages of Different Test Strategies (SAP, SITA, FDT SWAP, etc.)?

SAP is now the preferred method for performing visual field testing, and it has undergone the greatest amount of evaluation. In this view, SAP represents the clinical standard of care for visual field evaluation of glaucoma and other ocular and neurologic disorders, and it provides a means of information transfer among eye care practitioners. As outlined in Sect. 15.1, SITA and other forecasting test strategies (ZEST, TOP, GATE) are able to provide information that is essentially equivalent to the results found with previous test procedures with the advantage that they provide it in a fraction of the time and with slightly lower test–retest variability [2–4]. FDT, SWAP, and other test procedures are able to evaluate the integrity of subsets of neural visual elements, thereby providing a more specific and detailed description of damage produced by glaucoma or other ocular or neurologic disorders [2–4, 6–14]. It should be noted that the methods extending beyond SAP are not intended to be a replacement for SAP, but rather to be supplements to SAP for cases in which their results may provide insights as to severity of the disease, damage to specific mechanisms, and efficacy of treatment. The utility of their use is thus patient specific and dependent upon the suspected pathophysiology.

Summary for the Clinician

- SAP (white-on-white perimetry) testing is the clinical standard of care.
- Forecasting test strategies—SITA, ZEST, TOP, GATE—provide equivalent information to older threshold staircase strategies in less time and with less patient variability.
- Different tests of the visual system—FDT, SWAP, HPRP, RBP, etc.—evaluate subsets of neural visual elements. They are not meant to replace SAP but can supplement SAP results.

15.3 Is There a Visual Field Program of Choice at This Point in Time?

As indicated in Sects. 15.1 and 15.2, many options are available for obtaining visual field information. Most eye care practitioners use a forecasting threshold estimation test strategy that evaluates the central visual field, for example, the Humphrey 24-2 SITA Standard test procedure, or an equivalent test on a different automated perimeter (i.e., Octopus G2 TOP). For patients with limited attention spans or other special circumstances, it may be necessary to use a faster and/or less rigorous test procedure (e.g., Humphrey 24-2 SITA Fast). If assessments of the far peripheral visual field, the macular region, or other specific areas of the visual field are

necessary for clinical diagnostic purposes, then different test programs should be utilized as listed in Sect. 15.1. Finally, specialized visual field testing for evaluation of color vision mechanisms, spatial characteristics or temporal properties may also be important for a thorough clinical evaluation.

Summary for the Clinician

- No one test is ideal for every patient.
- Forecasting threshold estimation strategies (HFA 24-2 SITA Standard or Octopus G2 TOP) are most often used because they save time without sacrificing reliability of test results.
- Other tests may be chosen depending on an individual patient's needs.

15.4 What Visual Field Program Is Best for Use in a Glaucoma Subspecialty Clinic?

The most common visual field test procedure that is used for glaucoma patients and glaucoma suspects is a 24-2 test pattern using the SITA Standard threshold estimation procedure [2]. This provides good general coverage of the central (24° radius) visual field and will detect and evaluate most glaucomatous visual field deficits. Additionally, it is able to provide nearly all of the information that can be determined using the Full Threshold staircase procedures at a fraction (50–80 %) of the time. Some practitioners are interested in further reducing the visual field testing time and they use the SITA Fast procedure [15]. It should be noted, however, that SITA Fast produces greater patient response variability [16]. Comparable techniques are also available on other automated devices [2–4]. In some instances, specific glaucomatous visual field defects (temporal wedges, subtle nasal steps) will be missed by the 24-2 procedure, and some glaucomatous defects (e.g., arcuate defects) may be difficult to distinguish from artifactual test results (e.g., trial lens rim artifacts), and in these instances a 30-2 test procedure may be more useful. Infrequently, the initial glaucomatous defect may occur in the far periphery beyond the 30° radius, making it necessary to perform testing of the far peripheral visual field. There are also some cases in which other aspects of the eye examination provide a strong suspicion of glaucomatous damage, but conventional visual field testing is within normal limits. In these cases, specialized testing such as FDT perimetry [13, 14], short wavelength automated perimetry (SWAP) [6, 7], high-pass resolution perimetry (HPRP) [8], or RBP [9] may be a useful adjunct to other tests. Finally, for patients with limited cooperation and attention skills, there are other procedures that can be used, as outlined in Sect. 15.7 below.

Summary for the Clinician

- For a glaucoma clinic, a 24-2 SITA Standard threshold estimation procedure (or equivalent) is the most commonly used as it will detect most glaucomatous visual field defects.
- SITA Fast procedures take less time but result in more variable patient responses.
- The 30-2 test pattern takes a little more time to complete but may detect defects missed by a 24-2 test pattern, such as temporal wedge defects and subtle nasal steps, and it may distinguish some artifactual test results from true defects.

15.5 What Program is Best for Use in a General Clinic to Screen for Glaucoma?

When performing a screening test, for glaucoma or any other ocular or neurologic condition, there is always a trade-off between accuracy and efficiency. The large number of screening procedures that are available for automated perimetry produces a large series of choices for the eye care practitioner. On the one hand, it is possible to

select a procedure that has high specificity (minimizes the number of times that an individual with normal visual function is incorrectly classified as having glaucomatous damage) at the cost of reducing sensitivity (incorrectly classifying a person with glaucomatous damage as having normal visual function). On the other hand, one can select a procedure that has high sensitivity at the cost of reducing specificity. Selecting an appropriate visual field screening procedure depends on the particular needs of the eye care practitioner, the characteristics of his/her clinic population, and the amount of time available for testing. One procedure that appears to be especially useful to screen for glaucomatous visual field loss is the FDT perimeter. It has two screening procedures, one that is designed to optimize sensitivity and another that is designed to enhance specificity [17]. Additionally, there are decision rules that have been established for evaluation of FDT visual field screening results [18]. To date, it has been determined that good performance for screening can be achieved with this device using a test that takes between 30 and 90 s per eye to perform [19].

Summary for the Clinician

- The FDT perimeter has been found to be useful to screen general populations for glaucomatous visual field defects.

15.6 How Can I Convert from One Visual Field Strategy to Another to Help Me Interpret and Compare Tests?

Most eye care practitioners have found that it is often a straightforward matter to qualitatively convert from one visual field strategy to another, but it gets very complicated to do so, on a quantitative basis. One of the major advances afforded by automated perimetric testing has been the ability to immediately compare a patient's test results with the distribution of values obtained from a normal population (adjusting for typical aging effects, visual field location differences, and related issues). This allows comparisons to be made from one procedure to another in a straightforward manner, although it should be kept in mind that each normative database will be slightly different. Additionally, the use of probability levels and percentiles provides a means of evaluating visual field data in a manner that is less dependent on specific test conditions and measurement values. For progression, the availability of a database containing repeated testing of patients with varying levels of damage (usually with glaucomatous visual field loss) can also be helpful. Finally, many practitioners have found that the best method of switching from one procedure to another is to test the patient with the older procedure and to then begin a new series of testing with the new procedure at the same visit. In this manner, it is possible to establish a new baseline with the latest test procedure.

Summary for the Clinician

- Qualitatively it is straightforward to convert from one visual field strategy to another.
- Comparing probability levels and percentiles between different test types can be useful, although the normative databases may not be equivalent.
- If a switch of test procedures is planned, at the same visit test the patient on the old and new visual field procedure in order to establish a new baseline.

15.7 What Can be Done to Obtain Visual Field Information in a Patient Who Consistently Tests Unreliably?

Fortunately, most glaucoma patients are able to perform automated static threshold perimetry in a consistent and reliable manner, provided that proper test procedures are conducted [1–3]. In the

Ocular Hypertension Treatment Study (OHTS), the Optic Neuritis Treatment Trial (ONTT), and other multicenter clinical trials, enrolled patients were able to perform consistent, reliable visual fields approximately 95 % of the time [20–22]. However, there are some populations that are not able to perform reliable automated static perimetry tests. In these instances, kinetic testing (using the Goldmann perimeter, tangent screen, or Octopus semi-automated perimeter) may be helpful in providing appropriate visual field information because these procedures are more flexible and interactive. For large visual field deficits, confrontation visual field testing can also be performed, using a variety of techniques [23]. Procedures such as FDT perimetry are able to perform rapid and reliable visual field screening, and this is useful in populations that are difficult to test, such as children and patients with limited attention and cooperation skills [24]. There have been recent developments in more "objective" forms of visual field testing that impose fewer demands on the cooperation of the patient. These new techniques include pupil perimetry [25], multifocal electroretinograms (mfERG), and multifocal visual evoked potentials (mfVEPs) [26] (see Chap. 21 for explanation of test of VEP and mfERG). Pupil perimetry records pupillary responses to light stimuli presented at different visual field loci; it has limited sensitivity since the stimulus must be large and bright to elicit a response. Finally, if none of these procedures is able to provide reliable, clinically relevant visual field information, then diagnosis and monitoring of the patient must be obtained using other clinical methods (intraocular pressure, optic disc evaluation, comprehensive eye examination, review of medical and social history, treatment regimen and response, etc.).

Summary for the Clinician

- Most patients can successfully perform automated static threshold testing.
- For those patients who cannot successfully be tested on the usual tests, other options are available, such as kinetic testing and confrontation visual fields.
- FDT has been shown to be useful in patients with limited attention and cooperative skills, such as children.
- Objective tests require the least cooperation of the patient and include pupil perimetry, multifocal electroretinograms, and multifocal visual evoked potentials.

References

1. Anderson DR, Patella VM. Automated static perimetry. St. Louis: Mosby; 1999.
2. Bengtsson B, Olsson J, Heijl A, et al. A new generation of algorithms for computerized threshold perimetry, SITA. Acta Ophthalmol Scand. 1997;75:368–75.
3. Anderson AJ, Johnson CA. Comparison of the ASA, MOBS and ZEST threshold methods. Vision Res. 2006;46:2403–11.
4. Gonzales de la Rosa M, Morales J, et al. Multicenter evaluation of tendency-oriented perimetry (TOP) using the G1 grid. Eur J Ophthalmol. 2003;13:32–4.
5. Weijland A, Fankhauser F, Bebie H, Flammer J. Automated perimetry. Visual field digest. 5th ed. Koeniz: Haag streit; 2004.
6. Demirel S, Johnson CA. Short wavelength automated perimetry (SWAP) in ophthalmic practice. J Am Optom Assoc. 1996;67:451–6.
7. Racette SPA. Short wavelength automated perimetry. In: Sample PA, Girkin CA, editors. Ophthalmology clinics of North America. Philadelphia: W.B. Saunders; 2003. p. 227–36.
8. Frisen L. High pass resolution perimetry. A clinical review. Doc Ophthalmol. 1993;83:1–25.
9. Frisen L. New, sensitive window on abnormal spatial vision: Rarebit probing. Vision Res. 2002;42:1931–9.
10. McKendrick AM, Johnson CA. Visual perception: temporal properties of vision. In: Alm A, Kaufmann P, editors. Adler's physiology of the eye. St. Louis: C.V. Mosby; 2002. p. 511–30.
11. Quaid PT, Flanagan JG. Defining the limits of flicker-defined form: effect of stimulus size, eccentricity and number of random dots. Vision Res. 2005;45:1075–84.
12. Wall M. What's new in perimetry. J Neuroophthalmol. 2004;24:46–55.
13. Anderson AJ, Johnson CA. Frequency-doubling technology perimetry. In: Sample PA, Girkin CA, editors. Ophthalmology clinics of North America. Philadelphia: W.B. Saunders; 2003. p. 213–25.
14. Anderson AJ, Johnson CA, Fingeret M, et al. Characteristics of the normative database for the

Humphrey matrix perimeter. Invest Ophthalmol Vis Sci. 2005;46:1540–8.
15. Bengtsson B, Heijl A. SITA Fast, a new rapid perimetric threshold test. Description of methods and evaluation in patients with manifest and suspect glaucoma. Acta Ophthalmol Scand. 1998;76:431–43.
16. Artes PH, Iwase A, Ohno Y, et al. Properties of perimetric threshold estimates from Full Threshold, SITA Standard and SITA Fast strategies. Invest Ophthalmol Vis Sci. 2002;43:2654–9.
17. Johnson CA, Wall M, Fingeret M, Lalle P. A primer for frequency doubling technology perimetry. Skaneateles, New York: Welch Allyn; 1998.
18. Gardiner SL, Anderson DR, Fingeret M, et al. Evaluation of decision rules for frequency doubling technology (FDT) screening tests. Optom Vis Sci. 2006;83:432–7.
19. Johnson CA, Cioffi GA, Van Buskirk EM. Evaluation of two screening tests for frequency doubling technology perimetry. In: Wall M, Wild JM, editors. Perimetry Update 1998/1999. Amsterdam: Kugler; 1999. p. 103–9.
20. Keltner JL, Johnson CA, Beck RW, Group ONS, et al. Quality control functions of the Visual Field Reading Center (VFRC) for the Optic Neuritis Treatment Trial (ONTT). Control Clin Trials. 1993;14:143–59.
21. Keltner JL, Johnson CA, Spurr JO, Group OHS, et al. Confirmation of visual field abnormalities in the Ocular Hypertension Treatment Study (OHTS). Arch Ophthalmol. 2000;118:1187–94.
22. Keltner JL, Johnson CA, Cello KE, et al. Visual field quality control in the Ocular Hypertension Treatment Study (OHTS). J Glaucoma. 2007;16:665–9.
23. Johnson CA, Keltner JL. Principles and techniques of the examination of the visual sensory system. In: Miller NR, Newman NJ, editors. Walsh and Hoyt's textbook of neuro-ophthalmology. Baltimore: Lippincott Williams & Wilkins; 1998. p. 153–235.
24. Quinn LM, Wheeler DT, Gardiner SK, et al. Frequency doubling technology (FDT) perimetry in normal children. Am J Ophthalmol. 2006;142:983–9.
25. Hong S, Narkiewicz J, Kardon RH. Comparison of pupil perimetry and visual perimetry in normal eyes: decibel sensitivity and variability. Invest Ophthalmol Vis Sci. 2001;42:957–65.
26. Hood DC, Greenstein VC. Multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma. Prog Retin Eye Res. 2003;22:201–51.

Visual Fields: Fluctuation and Progression

16

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Core Messages

- Test-retest visual field fluctuation, which is seen both in normal and glaucoma patients, can confound the assessment of progression.
- True progression is likely if consecutive tests show reproducible defects in the same location.
- More frequent visual field testing is recommended in the first years of follow-up to help establish a consistent baseline and to assess whether or not disease is progressing.
- Deepening or enlargement of previous defects is a common form of progression. New defects usually are associated with worsening of previous defects.
- Automated progression analysis programs, such as the guided progression analysis (GPA) and visual field index (VFI), have been developed to help determine the presence and rate of progression.

16.1 How Do I Distinguish Between Fluctuation and True Progressive Change on Visual Field Printouts?

The primary obstacle in detecting whether or not a glaucoma patient's visual field loss is progressing is to separate true progression from changes due to variability or fluctuation between tests. Fluctuation is defined as the variability in the response to the same stimulus that is not related to true disease progression. As visual field testing is a subjective examination, variable responses may be obtained each time the test is performed (long-term fluctuation) or even during the same test (short-term fluctuation). This variability has been the biggest drawback of visual field assessment, as variability can greatly confound interpretation of change. Fluctuation varies among patients and among sectors in the same visual field, and usually it increases with severity of disease. To detect true progression, we need to evaluate whether the observed change exceeds the expected fluctuation for a particular area. Many strategies have been developed to deal with this issue and will be reviewed in this chapter.

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16.1.1 Usual Pattern of Visual Field Progression in Glaucoma

Visual field progression in glaucoma may be seen as (1) the development of a new defect, (2) deepening or enlargement of a preexisting defect, and (3) less commonly, as diffuse loss of sensitivity. Most frequently, progression is identified as a deepening of a preexisting scotoma (as shown by various research studies), along with enlargement of the scotoma. In one study evaluating visual field progression in glaucoma, most cases showed deepening (86 %) or enlargement (23 %) of a previous scotoma, while none of the eyes developed new visual field defects in previously normal areas [1]. This highlights the importance of evaluating areas adjacent to existing scotomas when searching for visual field progression. However, these adjacent areas are also known to exhibit larger degrees of fluctuation, which makes identification of true progression more difficult. Diffuse sensitivity loss may also represent glaucoma progression, although it is usually accompanied by new defects or worsening of previous focal defects. Progressive diffuse loss that is isolated should always raise the suspicion of cataract progression (or other media opacities).

16.1.2 Visual Field Defects Need to Be Repeatable

Before concluding that a change in the visual field is a sign of progression, it is important to demonstrate that the defect is repeatable on subsequent visual fields. This is one of the most important aspects of evaluating visual field progression in glaucoma. On any given visual field of a nonprogressing patient, it is common to find a few scattered points with significant depression compared with old fields. Variable responses that do not reflect true progression will vary in location and pattern among consecutive tests, whereas a true defect reflecting further loss of ganglion cells will be repeatable. One cannot stress enough the value of confirming new visual field defects. Data from several clinical trials have suggested that change needs to be repeatable, with a defect of the same type in the same general location, on three consecutive examinations before progression can be confirmed [2–5].

16.1.3 Results of Visual Field Tests Should Be Correlated with Other Clinical Data

New or enlarged visual field defects should also be concordant with other clinical findings, such as those seen in the optic disc and retinal nerve fiber layer. To this end, several studies have used maps that correlate areas of the visual field with the corresponding optic disc sectors (Fig. 16.1) [6, 7]. Although visual field progression may be seen without detectable optic disc deterioration, disagreements between structure and function should prompt careful reevaluation. In advanced glaucoma, visual fields may detect changes that are not appreciated during examination of a severely cupped nerve. Although short- and long-term fluctuation increases in advanced cases of glaucoma, repeatable visual field progression, sometimes associated with a patient's perception of decreased acuity, may represent the only sign of progressive disease.

Summary for the Clinician

- Visual field fluctuation increases with disease severity.
- Visual field progression manifests (1) most frequently as deepening and/or enlargement of previous scotomas, (2) as a new defect, or (3) as diffuse sensitivity loss.
- Areas adjacent to existing scotomas exhibit the greatest amount of fluctuation, making it more difficult to establish true progression.
- Progressive diffuse loss can be due to media opacity or it can be due to glaucoma, but when due to glaucoma the

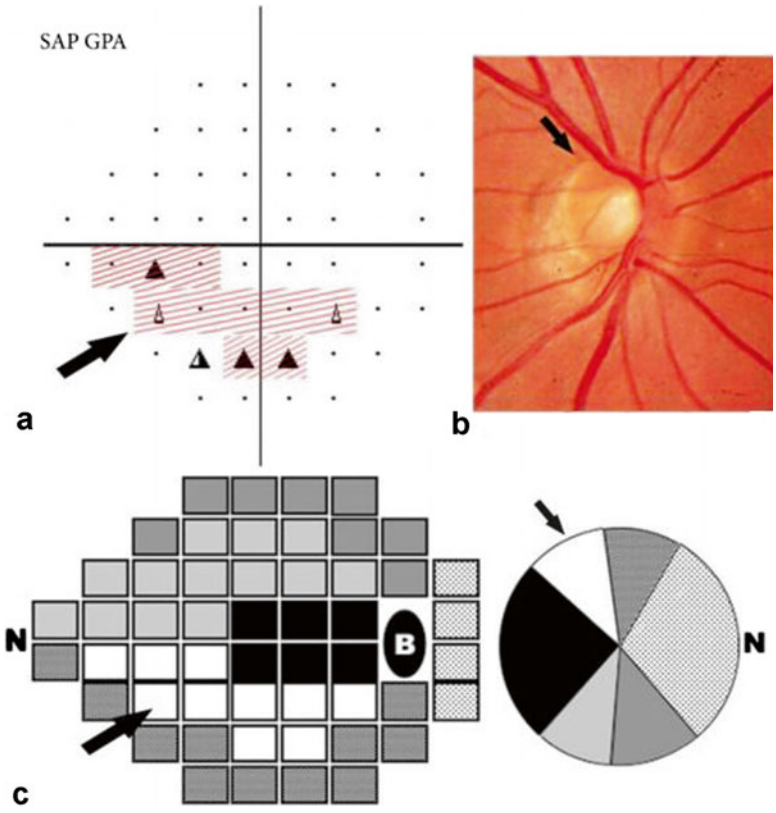

Fig. 16.1 Evaluation of visual field progression should always be correlated with structural assessment of the optic nerve and retinal nerve fiber layer. Several maps have been used to represent corresponding areas of the optic nerve and visual field. (**a**) SAP-guided progression analysis (GPA) showing progression in the inferior hemifield. (**b**) Optic disc photograph with rim thinning at the superior-temporal sector. (**c**) Example of a commonly used correlation map between sectors of the optic disc and sectors of the visual field (modified from [7])

loss is usually accompanied by a new or deepening existing defect.

- Change must be confirmed on subsequent examination to be called true progression (generally, it must be seen on at least three examinations).
- Progressive change should be correlated to other confirmatory findings.

16.2 How Frequently Should Visual Fields Be Tested?

The higher the variability on a series of examinations, the lower is our ability to detect progression. Therefore, it is important to reduce potential sources of variability on visual field tests. This can be achieved by educating the patient and selecting proper test strategy. Lower false-positive and fixation loss rates, as well as lower rates of testing artifacts, can be achieved if the technician provides the patient a good orientation of the test and its purpose. Choosing faster strategies, such as SITA (see Chap. 15), may also improve test performance and reduce variability due to fatigue. Unreliable tests should be repeated as soon as possible. High false-negative rates may represent distraction or fatigue, but they are also common in cases of advanced disease due to variability of the visual response in areas of sick retinal ganglion cells.

It is important to recognize that some patients need more frequent visual field testing than do others. Although most glaucoma patients under treatment will have a slow rate of progression over the years, there are those few who will have fast and disastrous progression rates. Published rates for mean deviation (MD) deterioration in glaucoma patients have been varied and depend on individual susceptibility, severity of disease, and treatment strategies. One should perform enough visual fields at the beginning of follow-up in order to detect cases that present with fast

progression rates. A recent study suggested six visual field examinations in the first 2 years, in order to rule out aggressive disease and to establish a consistent baseline [8]. Over time, the frequency of examinations may be reduced to once or twice yearly as long as no change is detected. At any time during follow-up that a change is identified on the visual field, one should not wait another year to proceed with confirmatory tests, but instead the frequency of examinations should again be increased in order to confirm or exclude progression as soon as possible.

In a recent publication, Chauhan et al. [8] demonstrated the value of repeated examinations to detect progression. They observed that the higher the test variability, the longer time it takes to detect significant progression, and that slower rates of progression require more years of follow-up for detection. The authors also observed that increasing the number of tests per year favored detection of progressive loss. However, although increasing the frequency of tests is desirable in order to detect progression, the frequency of visual field testing is constrained by insurance companies, clinicians' workflow, and patient availability and cooperation. Therefore, it is important for clinicians to identify patients who are at higher risk for disease progression, so that more visual fields can be obtained in these specific cases. A recent report from the Early Manifest Glaucoma Trial has suggested that more severe disease, higher intraocular pressure levels, thin corneas, and the presence of exfoliation are risk factors for faster visual field progression in patients with glaucoma.

Summary for the Clinician

- Minimize patient sources of variability because high variability makes detection of progression more difficult.
- It is important to perform enough visual fields in the first years of follow-up to rule out rapidly progressing disease and to establish a consistent baseline. After this period, the frequency of visual field examinations may be reduced to once or twice a year, as long as no change is detected.
- When visual field progression is suspected, it is important to repeat the test as soon as possible in order to confirm or exclude true deterioration.

16.3 What Are the Methods Available for Determining Visual Field Progression?

There are two main approaches to analyze progression—event-based and trend-based analyses. The first approach compares the current examination with a previous one (usually the baseline test). If the results are significantly worse on the follow-up examination, progression is indicated. This is called *event-based analysis*, as it looks for defects on the current examination that were not present on a previous examination. In the second approach, instead of only comparing a few tests, one looks for progressive change by analyzing all the tests available in a specific period of time. This is called *trend-based analysis*, as a trend in the values is plotted over time, and significant deterioration can be assessed by observing the slope or decline of the regression line. Aside from evaluating whether progression has occurred, trend-based analysis also allows an estimation of the rate of progression. It is well known that some patients deteriorate faster than others, and estimating each individual's rate of progression is helpful in evaluating the necessary aggressiveness of treatment and the response to therapy.

Summary for the Clinician

- Progression can be detected by event-based analysis in which the current visual field test is compared with a set of baseline tests and the appearance of any new defects or worsening of previously existing defects is detected.

- Progression may also be detected by trend-based analysis in which the trend over time on a series of tests is plotted allowing for the calculation of the rate of progression.

16.4 What Automated Progression Analysis Software Is Available to Help with Visual Field Interpretation?

Different analytical tools have been developed to assist clinicians in identifying visual field progression. The most general and simple tool is the MD index plotted against time. Any significant decline in MD indicates progressive deterioration. However, even though deterioration on the MD may represent glaucomatous progression, it may also represent progressive media opacity from cataract. Conversely, cataract extraction in a glaucomatous patient may mask progression when evaluated by the MD because the MD will improve after removal of the cataract.

Another analytical tool incorporated into previous Humphrey perimeter versions is the *Glaucoma Change Probability (GCP)* software. The GCP performs individual comparisons of each visual field point on follow-up examinations with a set of baseline fields. Progression is flagged if two or more adjacent points within or adjacent to an existing scotoma show significant deterioration confirmed on two consecutive tests. The GCP performs a very individualized analysis of the sectors in the visual field; however, as it is based on the total deviation plot, it may still be affected by diffuse media opacities such as cataract.

The new *Guided Progression Analysis (GPA)* software was developed to overcome most of the limitations mentioned above. Both the GCP and the GPA are event-based analyses, but the GPA has several potential advantages when compared with the GCP. The GPA is based on the pattern deviation plot, as opposed to the total deviation plot used by the GCP. Therefore, the GPA evaluates progression adjusted for diffuse effects. In addition, the GPA runs not only on SITA tests, but also accepts full-threshold tests for the baseline pair (the GCP did not), which is convenient as some patients with long-term follow-up have been tested with the full-threshold strategy during early follow-up. As detection of new or progressing visual field defects is performed by comparison to the baseline, it is critical to have reliable baseline examinations. The software automatically selects the first two available examinations as the baseline tests. However, one can easily override this automatic selection to a more suitable time-point (e.g., change in therapy after progression), or to reject fields that are unreliable due to initial learning effects (which could reduce the sensitivity to detect progression). Figure 16.2 exemplifies the importance of setting the proper baseline. The GPA software then compares each follow-up test to the average of the baseline tests. It identifies points that show change greater than the expected variability (at the 95 % significance level), as determined by previous studies with stable glaucoma patients. If significant change is detected in at least three points, and is repeated in the same points over two consecutive follow-up tests, then the GPA software will flag the last examination as *Possible Progression*. If the same three or more points have significant change detected and repeated in three consecutive follow-up tests, the GPA software will flag the last examination as *Likely Progression*. Figures 16.2 and 16.3 illustrate examples of progression detected by the GPA.

The most recent version of the Humphrey field analyzer also provides the *visual field index (VFI)* and VFI progression plot. The VFI is a newly developed index that is proposed to better evaluate the rate of progression with SAP. The aim of this analysis is not to detect progression, which can be done with the GPA itself, but to provide valuable information on the rate of deterioration. The VFI is calculated as the percentage of normal visual field, after adjustment for age. Therefore, a VFI of 100 % represents a completely normal visual field, while a VFI of 0 % represents a perimetrically blind visual field. The VFI is shown on the GPA printout both as a percent value for each individual examination and as a trend analysis, plotted against age (Fig. 16.4).

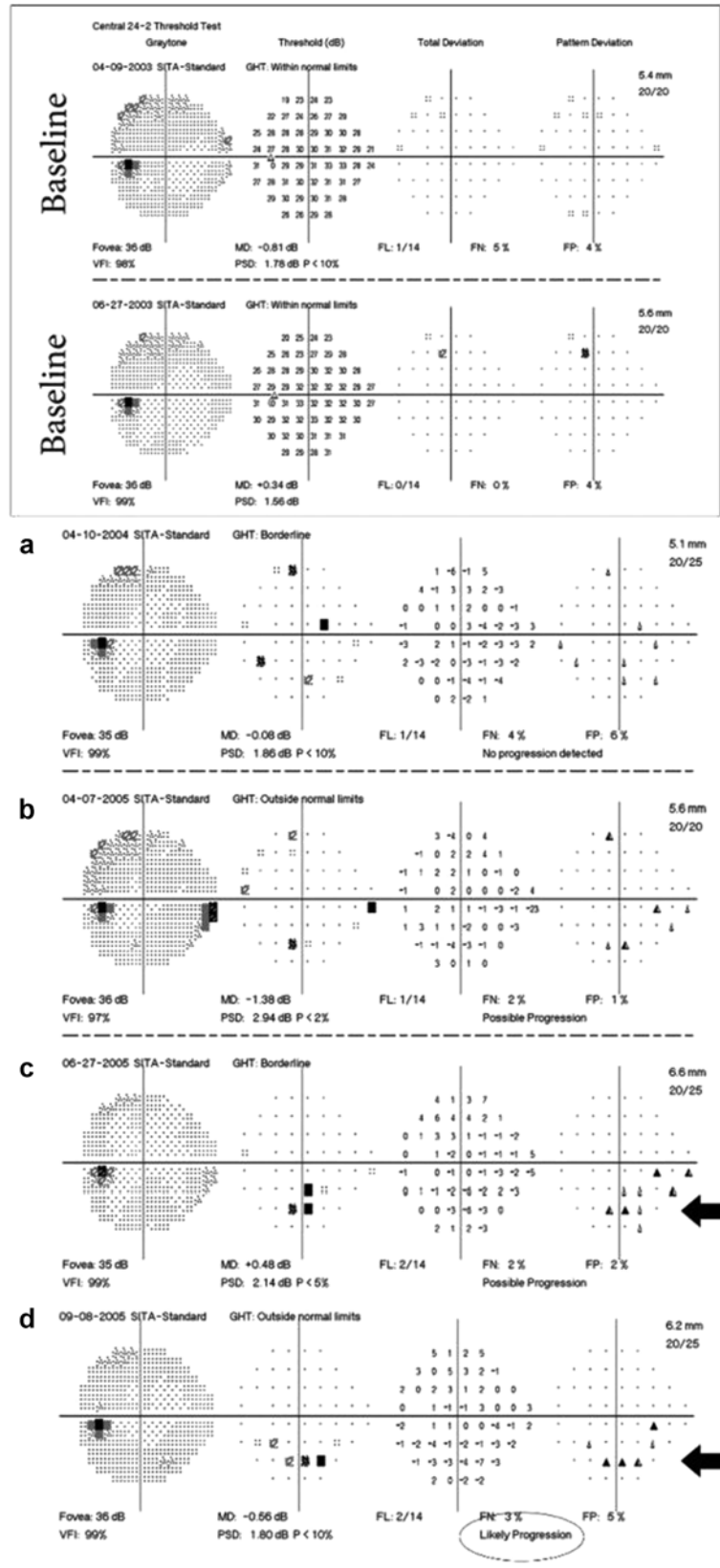

Fig. 16.2 SAP SITA GPA of a glaucomatous patient followed for over 2 years. The first two images were selected as baselines. Every follow-up examination is compared with the average of the two baseline tests. (**a–d**) Represent consecutive follow-up examinations, in which several points are flagged as showing significant deterioration. Some of these changes are not repeatable on consecutive tests. However, a group of points on the inferior hemifield consistently show deterioration and are ultimately flagged as *Likely Progression. Note* that the new defect follows a typical nerve fiber layer bundle pattern

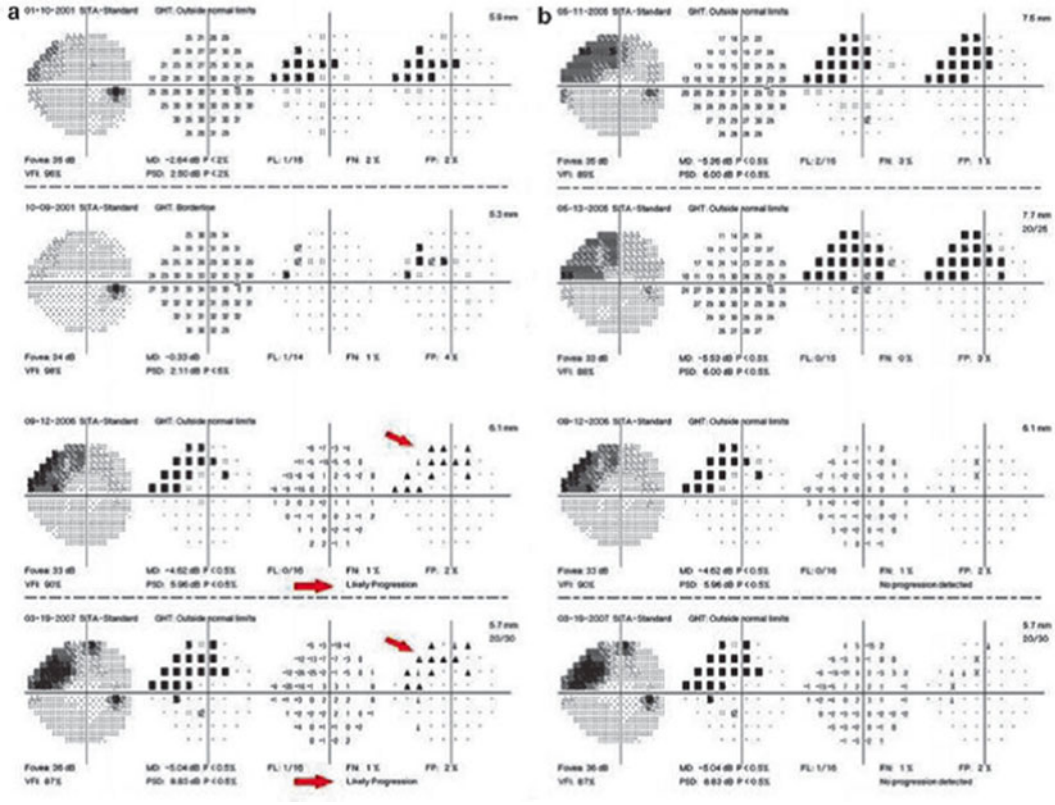

Fig. 16.3 The baseline for the GPA must always be reset after interventions to stop progression. (**a**) Baseline examinations are from 2001, and abnormality was first detected in 2005. There were also several examinations in between (not shown). The patient underwent trabeculectomy to lower intraocular pressure in 2005. (**b**) The new baseline was set to 2005 in order to detect if further progression has occurred from 2005 to 2007. No evidence of progression was detected in the most recent tests compared with those of the 2005 baseline

While the MD is based only on the total deviation map, and thus is largely affected by cataract, the VFI is based both on the pattern deviation and the total deviation probability maps. The former (pattern deviation) helps in the identification of possibly progressing points, and the latter (total deviation) is used for the actual calculation of change of the total deviation value [9]. In addition, the VFI algorithm uses different weights for different locations, giving more weight to the central points, which have higher impact on the patient's quality of vision. The final VFI score is the mean of all weighted scores. A recent study by Bengtsson and Heijl [9] showed that the new summary index performed similarly to the MD for patients without cataract. For glaucoma patients with worsening cataract, however, the VFI showed a slower rate of progression than the MD, which supposedly would be a more accurate representation of the actual rate of glaucoma progression. Conversely, for glaucoma patients who had cataract surgery during follow-up, the VFI showed a higher rate of progression compared with the MD. While the improvement in media clarity masked glaucoma progression when assessed by the MD, this did not happen when assessment was performed with the VFI.

The VFI also provides an estimate of the additional visual field loss that will occur in the next 5 years, assuming that the same rate of progression is maintained. This is valuable for the clinician as it estimates the number of years that a specific patient has before advancing to a perimetrically blind visual field if no further action is taken to improve control of the disease (see Table 16.1 for comparison of tools).

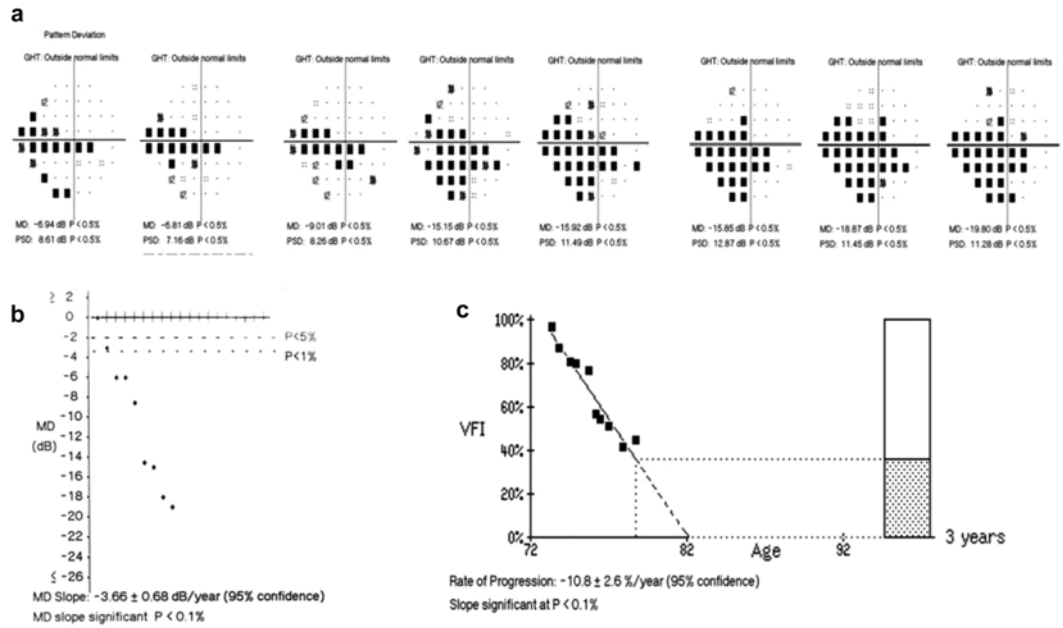

Fig. 16.4 Example of a patient with progressive visual field loss. (**a**) Sequential view of pattern deviation probability plots showing deepening and enlargement of the defect. (**b**) Mean deviation (MD) index plot showing significant deterioration over time, with loss at a rate of 3.66 dB/year. (**c**) Visual field index (VFI) plot showing significant deterioration over time. The rate of progression is given as a percentage, with loss at a rate of 10.8 % per year. In addition, the VFI plot shows an estimate that the patient will be perimetrically blind at the age of 82 years if the same rate of progression is maintained. At the *right side* of the VFI plot is the VFI bar, which indicates on a 100 % scale of "normality" the current status of the patient and the estimate of his status after 3 years. The *dotted area* determines the proportion of visual field that is within the expected normal limits of sensitivity (the lower the dotted area, the more severe the visual field loss)

Table 16.1 Automated progression analysis

Analytical tool	Index plot used for analysis	Analysis	Progression defined as…
Mean deviation (MD) plotted against time	Mean deviation	Plots MD values over time	Decrease in MD over time
Glaucoma change probability	Total deviation	Compares individual field points at follow-up to baseline	Two or more adjacent points in or next to an existing scotoma show a significant deterioration on two consecutive tests
Guided progression analysis	Pattern deviation	Compares each follow-up test to the average of the two baseline tests; identifies points that show change at the 95 % significance level	Possible progression = significant change in at least three points that is repeated over two consecutive tests; likely progression = significant change in at least three points that is repeated over three consecutive tests
Visual field index	Mean deviation and pattern deviation	Provides information on the rate of progression; gives more weight to central visual field points	Provides an estimate of additional field loss that will occur over the next 5 years given a steady rate of deterioration

Summary for the Clinician

- The GPA is a clinically useful tool for evaluating visual field progression. It provides a comparison of follow-up examinations to a pair of baseline examinations, taking into account the estimated variability between tests.
- The VFI is a new parameter designed to provide a more clinically useful estimate of the rate of glaucoma progression. It also provides an estimate of the number of years before a perimetrically blind visual field develops, given the same rate of progression is maintained.

References

1. Boden C, et al. Patterns of glaucomatous visual field progression identified by three progression criteria. Am J Ophthalmol. 2004;138(6):1029–36.
2. Heijl A, et al. Measuring visual field progression in the Early Manifest Glaucoma Trial. Acta Ophthalmol Scand. 2003;81(3):286–93.
3. The Advanced Glaucoma Intervention Study (AGIS). 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130(4): 429–40.
4. Keltner JL, et al. Confirmation of visual field abnormalities in the Ocular Hypertension Treatment Study. Ocular Hypertension Treatment Study Group. Arch Ophthalmol. 2000;118(9):1187–94.
5. Kim J. The Advanced Glaucoma Intervention Study (AGIS): 14. Distinguishing progression of glaucoma from visual field fluctuations. Ophthalmology. 2004;111(11):2109–16.
6. Ferreras A, et al. Mapping standard automated perimetry to the peripapillary retinal nerve fiber layer in glaucoma. Invest Ophthalmol Vis Sci. 2008;49(7): 3018–25.
7. Garway-Heath DF, et al. Mapping the visual field to the optic disc in normal tension glaucoma eyes. Ophthalmology. 2000;107(10):1809–15.
8. Chauhan BC, et al. Practical recommendations for measuring rates of visual field change in glaucoma. Br J Ophthalmol. 2008;92(4):569–73.
9. Bengtsson B, Heijl A. A visual field index for calculation of glaucoma rate of progression. Am J Ophthalmol. 2008;145(2):343–53.

Visual Fields: Field Interpretation

17

Balwantray C. Chauhan

Core Messages

- The visual field analyses and printouts contain invaluable information. All portions of the printout should be used to make clinical decisions.
- Special attention should be given to examination quality.
- For individual patients, the various statistical analyses are guidelines to help the clinician.

17.1 How Is Information on a Single Field Printout of the Humphrey Field Analyzer Interpreted?

The individual (or single field) printout (Fig. 17.1) contains a wealth of information to help clinicians decide whether the visual field is abnormal and specifically the likelihood of it being a glaucomatous visual field. The printout can be divided into four convenient parts to aid interpretation (Fig. 17.1).

17.1.1 Part 1 of the Visual Field Printout

This section of the printout (see Fig. 17.1) contains the demographic, test type and performance data. The name, eye, date of birth, and test date should be verified before interpreting the printout. The visual acuity and refractive correction used should also be checked.

Interpretation depends on the type of test, hence it is imperative that this information is carefully checked. In this case (Fig. 17.1), the test type is the central 24-2 threshold test with a Goldmann size III stimulus and the SITA (Swedish Interactive Threshold Algorithm) Standard examination strategy. Other test patterns (e.g., 30-2 or 10-2), examination strategies (e.g., full threshold or SITA-Fast), or stimulus sizes (e.g., size V) can also be used.

The blind spot monitor can be turned on or off as can the gaze tracking monitor (trace shown at bottom of printout). These indices can help in determining the fixation reliability of the patient.

There are three reliability indices printed in Part 1, namely

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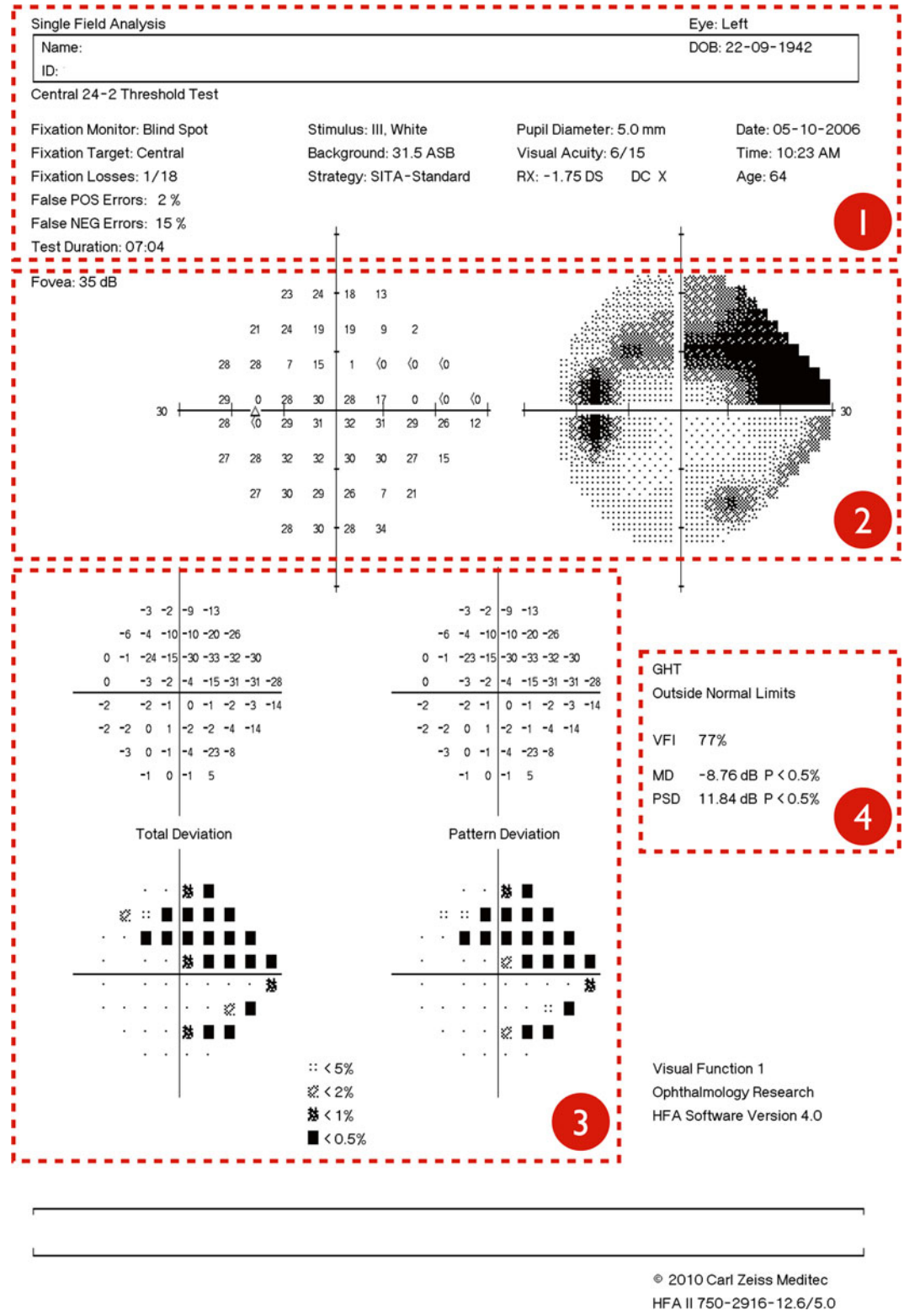

Fig. 17.1 The single visual field printout from the Statpac program of the Humphrey Field Analyser. The printout is divided into four parts: (1) the demographic, test type and performance data; (2) the sensitivity and gray-scale plot; (3) the total and pattern deviation analyses and (4) the summary indices

1. *Fixation losses* (the frequency of positive responses when a bright stimulus is presented in the blind spot),
2. *False positive errors* (the estimated number of times, expressed as a percentage, the response button is pressed when no stimulus is presented, or responds impossibly fast after stimulus presentation) and
3. *False negative errors* (the estimated number of times, expressed as a percentage, the response button is not pressed when a stimulus of much brighter intensity than threshold is presented at a location tested earlier in the session).

These indices are only a guide to indicate patient reliability. Fixation errors can be high in spite of good fixation accuracy, for example if the blind spot is small, or if it is not optimally located prior to initiating the test. The technician's notes (if available) or the gaze tracking monitor trace should also be consulted. A high false-positive rate is an indication that the patient may be anxious and "trigger happy." A test with a high false-positive rate (>20 %) may be unreliable, particularly if the test duration is especially long, or if the foveal or macular sensitivity values (shown in Part 2) are especially high.

17.1.2 Part 2 of the Visual Field Printout

This section of the printout (see Fig. 17.1) contains the foveal sensitivity (if measured), the individual sensitivities of the test locations measured in decibels (dB) and the interpolated gray-scale plot of the sensitivity values. Values with <0 dB indicate that the patient did not respond to a stimulus of maximal intensity. Although the gray scale provides a quick overview of the location of defects, it should not be relied on exclusively because of the extensive interpolation of the gray scales between locations not actually tested.

17.1.3 Part 3 of the Visual Field Printout

This section of the printout (see Fig. 17.1) contains two important measurements of visual field loss, namely total deviation and pattern deviation. The total deviation values shown for each location (top left of Part 3) indicate, in dB, the difference between the measured sensitivity and the expected sensitivity in an age-matched healthy individual. Hence, a total deviation value of −9 dB indicates that the measured sensitivity was 9 dB lower than normal, while a value of 2 dB indicates that the measured sensitivity was 2 dB higher than normal.

The pattern deviation values shown for each location (top right of Part 3) indicate the deviations from normal after adjusting for the general height of the visual field. The general height is reduced by cataract and small pupil size, however, it can also be reduced by diffuse or overall changes to the visual field. These values help the clinician evaluate the localized component of visual field damage after adjusting for loss that may occur because of cataract or diffuse loss. Hence a total deviation of −6 dB and a pattern deviation of −4 dB indicate that 2 dB of the loss is due to a reduction in general height at that location.

The total deviation probability plot (bottom left) indicates the probability of the total deviation value occurring in a normal population. A probability designation of <5 % indicates that the total deviation value at that location occurs in less than 1 in 20 normal subjects while a designation of <0.5 % indicates that the sensitivity at that location is so significantly reduced that it occurs in less than 1 in 200 normal subjects. Similarly, the pattern deviation probability plot (bottom right) indicates the probability of the pattern deviation values occurring in a normal population.

17.1.4 Part 4 of the Visual Field Printout

This section of the printout (see Fig. 17.1) contains the summary indices of the Glaucoma Hemifield Test (GHT), Visual Field Index (VFI), Mean Deviation (MD) and Pattern Standard Deviation (PSD). Since visual field asymmetry above and below the horizontal meridian is a hallmark of glaucomatous visual

field damage, the GHT compares the mean sensitivity in 5 mirror-image superior and inferior retinal nerve fiber layer sectors. If there is significant asymmetry in at least one of the mirror-image sectors occurring in < 1 % of the normal population, the GHT is marked as "Outside normal limits". If the asymmetry occurs in < 3 % of the normal population, the GHT is marked as "Borderline." If the asymmetry occurs in > 3 % of the normal population but the sensitivity of points is either too high or too low, occurring in < 0.5 % of the normal population, the GHT is marked as "Abnormally high sensitivity" or "Abnormally low sensitivity," respectively. In all other cases, the GHT is marked "Within normal limits."

The VFI is an index for estimating rates of visual field change expressed as a value from 100 % (normal) to 0 % (perimetrically blind) [1]. It disregards any sensitivity loss at a location unless associated with a pattern deviation probability of <5 %, however, with more advanced loss the calculation reverts to total deviation. The index places more emphasis on the central compared to the peripheral field. In this case (Fig. 17.1), it is 77 % in spite of a significantly damaged visual field.

The MD is a weighted mean of the total deviation values in the visual field, while PSD is the standard deviation of the total deviation values. Conceptually, MD indicates the overall amount of visual field damage. The probability of this value occurring in a normal population is less than 0.5 %, in the case of Fig. 17.1, where MD is −8.76 dB. PSD is the variability of the total deviation values, with typically high PSD in localized damage. In this case, the PSD is 11.84 dB and occurs at this value in less than 0.5 % of the normal population.

Summary for the Clinician

- The single field printout contains very useful information on the status of the visual field, its reliability, and various indices of abnormality.
- The clinician must pay special attention to the demographic and test performance data before interpreting the visual field.
- All portions of the printout contain important information and the clinician should not only rely on the gray-scale plot.

17.2 How Is the Information on the Glaucoma Progression Analysis Printout Interpreted?

The Glaucoma Probability Analysis (GPA) is a software package developed for analyzing serial visual fields in glaucoma and helps the clinician determine the likelihood of visual field progression [2]. It contains a mixture of trend-based (VFI over time) and event-based (pointwise analysis of the magnitude of change) analyses. The printout can be divided into three parts (Fig 17.2).

17.2.1 Part 1 of the GPA Printout

This section of the printout (see Fig. 17.2) displays the two baseline examinations that can be selected by the user to compare subsequent follow-up examinations. Each baseline examination is displayed in a concise manner and includes the gray-scale plot, the individual pointwise sensitivity values, the total and pattern deviation probability maps as discussed above. Additionally the results of the GHT, VFI, MD, PSD, and reliability criteria are provided. Care should be taken to ensure that the two baseline examinations are similar and representative of the visual field status to which subsequent comparisons are to be made. While the GPA will exclude obviously different visual fields due to learning effects, etc., it is important that baseline examinations are chosen with care.

17.2.2 Part 2 of the GPA Printout

This section of the printout (see Fig. 17.2) shows VFI over time and a regression analysis to

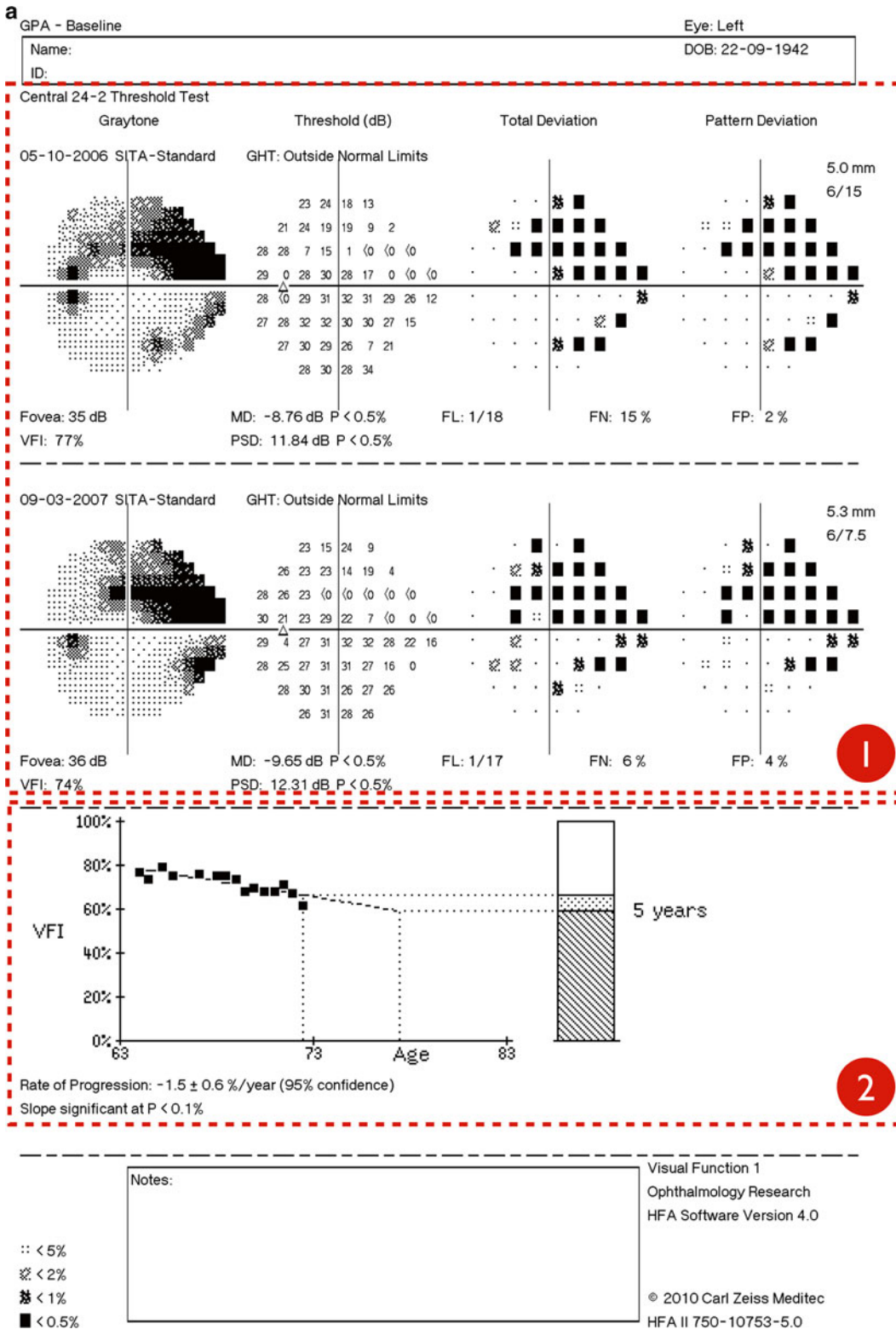

Fig. 17.2 (**a**) Serial visual field analysis with the Glaucoma Probability Analysis. The printout is divided into three parts: (1) baseline examinations; (2) Visual Field Index (VFI) plot showing rate of change over time and (**b**) (3) Follow-up examinations with pointwise analysis of pattern deviation change

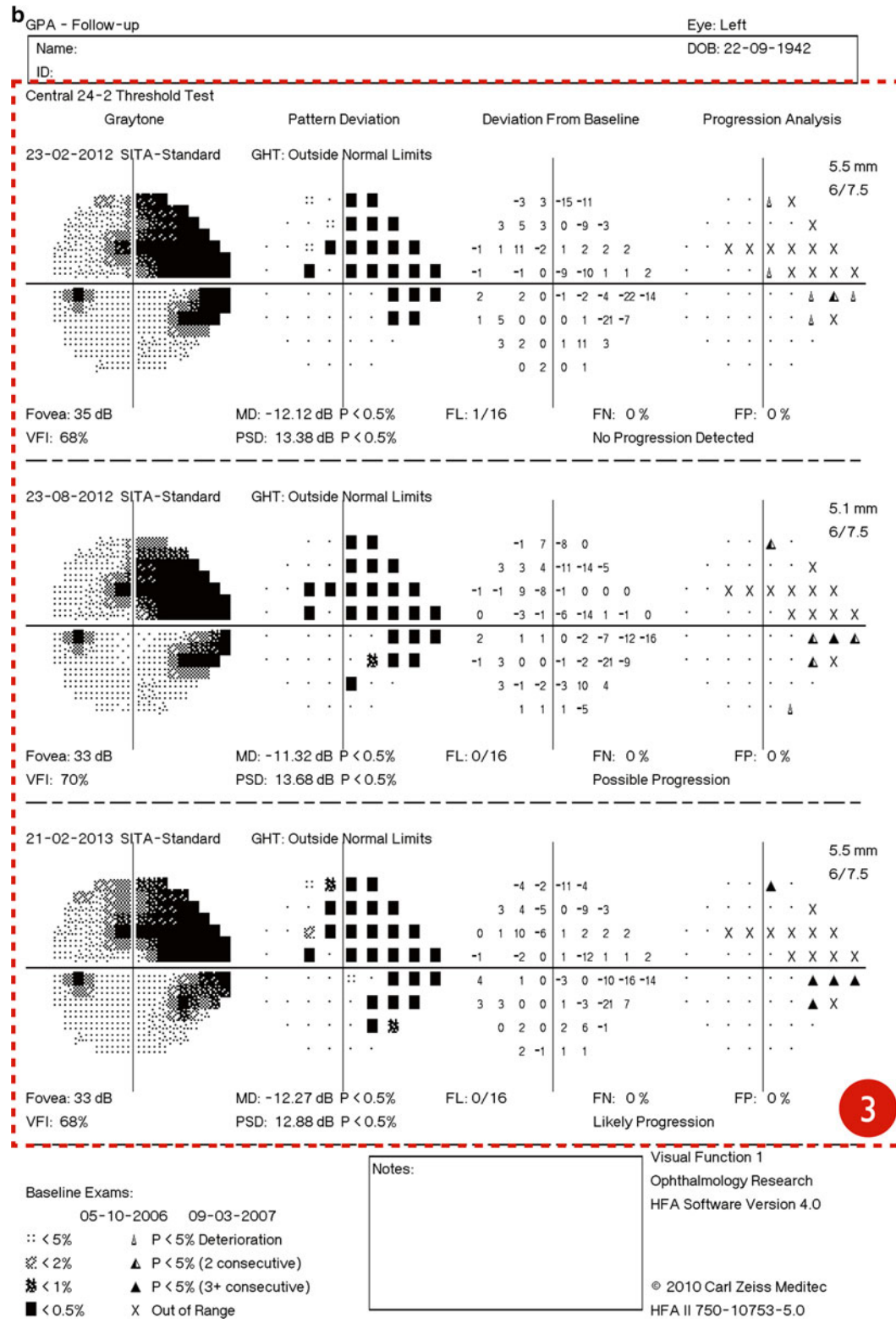

Fig. 17.2 (continued)

compute the rate of progression (in this case, −1.5 %/year), its 95 % confidence interval (±0.6 %/year) and statistical significance ($p < 0.1$ %). The analysis also projects the amount of VFI change in the next 5 years if the current rate of progression is maintained. Estimates of the rate of visual field loss are particularly useful in determining the likelihood of the patient encountering visual disability depending on age and level of visual field loss. Until recently rates of MD have been used for these calculations. While VFI is an intuitive index, there are concerns that it has reduced sensitivity in early damage compared to MD. Furthermore, VFI switches from utilizing the pattern deviation to using the total deviation in advanced loss, there are variable and nonlinear effects that can hamper the accuracy of rate estimates [3, 4]. Rate estimates become more precise with an increasing number of examinations, and many examinations are necessary to obtain meaningful slope values [5].

17.2.3 Part 3 of the GPA Printout

This section of the printout (see Fig. 17.2) displays each of the follow-up examinations. Up to 16 examinations can be displayed per analysis. The gray-scale plot and pattern deviation probability plot are shown with the results of the GHT, VFI, MD, PSD, and reliability indices.

The last two columns of the printout, "Deviation From Baseline" and "Progression Analysis" show analysis of the current examination compared to the mean of the two baseline examinations. The "Deviation From Baseline" plot shows the pointwise difference in pattern deviation from baseline; hence, a value of −6 dB indicates a 6 dB worsening of pattern deviation. The "Progression Analysis" indicates the likelihood of a given difference in pattern deviation arising from chance alone in a group of patients with the same level of visual field damage but who have not undergone progression. In other words, the probability values give an indication of whether the differences that are observed in follow-up examination can be due to test–retest variability only. A point marked with an open triangle indicates that the observed difference in pattern deviation at that location has < 5 % chance of occurring due to variability alone.

Naturally, diagnosis of progression requires confirmation of change. The GPA utilizes the visual field progression criteria employed in the Early Manifest Glaucoma Trial (EMGT) [6]. Points shown as bisected black and white triangles indicate locations at which significant change (probability of <5 %) in pattern deviation has occurred in two consecutive examinations. The presence of three or more bisected triangles indicates "possible progression." Points shown as solid black triangles indicate those with significant change (probability of < 5 %) has occurred in three or more consecutive examinations. The EMGT defined progression with the presence of three black triangles, consequently, the GPA flags these fields as having "likely progression." If the criteria for neither "possible progression" or "likely progression" are met, then the visual field is flagged as having "no progression detected."

In certain cases where damage is extensive, the GPA is unable to accurately determine the probability values to be assigned to changes in pattern deviation. This is an inherent limitation of static automated perimetry where variability limits of locations with large amounts of damage are underestimated because of limited stimulus intensity. In this case, locations are marked with a cross indicating "Out of Range" (Fig. 17.3).

Summary for the clinician

- The GPA printout provides a comprehensive analysis of visual field change.
- All portions of the printout should be examined carefully with special reference to examination selection and quality. Poor quality examinations (due to poor reliability learning effects, etc.) should be removed as they can seriously hamper the analysis.
- Two good quality baseline examinations are required for GPA.

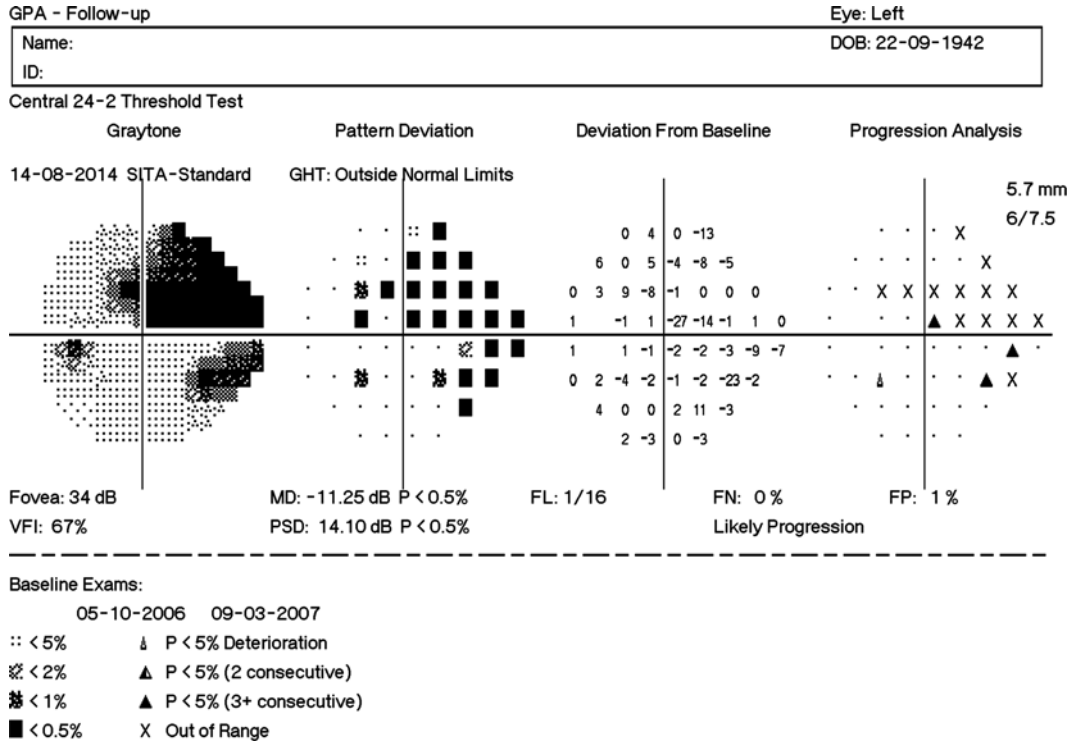

Fig. 17.3 Example of a Glaucoma Probability Analysis plot indicating that the probability of changes in pattern deviation cannot be computed in areas with high degrees of baseline visual field loss (indicated by the X, "Out of Range" symbols)

- The GPA contains both a trend-based analysis based on VFI change over time and an event-based analysis based on the magnitude of change at individual test locations.
- The VFI provides an intuitive estimate of visual field loss and rate of progression, however, care must be applied when used in early damage and in cases when MD straddles –20 dB.
- The GPA utilizes progression criteria set forth in the EMGT. These criteria do not take into consideration the location of significant visual field change, hence changes at central locations are not identified as carrying more clinical significance compared to mid-peripheral ones. The clinician must continue to exercise clinical judgment when interpreting these analyses.

17.3 What Are Pitfalls to Avoid in Interpretation of Visual Fields?

Pitfalls can be divided into several categories and should be avoided to ensure appropriate interpretation of the visual field.

17.3.1 Quality of Visual Field Examinations

Test quality is of paramount importance for the analysis of single or serial visual field analysis. There are several factors (see earlier) that may indicate poor quality. Examinations of poor reliability, those affected by learning effects, inattention, etc., should be removed. Inclusion of these examinations can seriously hamper the clinical evaluation of the visual field.

17.3.2 Automatic Reliance on the Statistical Analysis

Making clinical decisions based on statistical analyses alone should be avoided. Statistical analyses provide invaluable guidance on the status of the individual visual field and its progression. The analysis algorithms have undergone several revisions and are based on years of careful research. Nonetheless, they are not infallible. The analyses should be in alignment with clinical impressions and used as part of a multifactorial decision-making process.

Sudden and unexpected changes in the visual field should always be confirmed in subsequent examinations. Differences in the total and pattern deviation maps should be examined and gauged with the level of cataract or other suspected reasons for diffuse loss. Glaucomatous visual fields have at least a small component of diffuse loss [7–9] and the GPA may underestimate the degree of change [10].

In individual patients, criteria for progression in the GPA analyses are meant only as a guideline. There may be many situations where the GPA does not agree with clinical assessment. For example, if change occurs in only one or two locations, the GPA may not flag progression as having occurred; however, if flagged points are located close to fixation, this may actually be a clinically significant situation. On the other hand, the GPA may flag progression of noncontiguous locations or those in the mid-periphery, which are not as clinically concerning.

17.3.3 Visual Field Artifacts

Visual field artifacts can occur even in experienced test takers. These results should be removed from analyses and the test repeated. Common artifacts include: (1) upper lid defects because of ptosis or deeply set eyes; (2) lens rim defects from highly ametropic corrections and/or poor lens centration; (3) "clover-leaf" field in the gray-scale plot due to inattention or fatigue (the field has progressively reduced sensitivity as the visual field testing progresses); and (4) "white-field" in the gray-scale plot where the sensitivity is abnormally high. In this situation the fixation error and/or false positive rate may be high. Furthermore, the total deviation plot may be normal but the pattern deviation plot may show significant defects because of the abnormally high hill of vision.

17.3.4 An Adequate Number of Visual Field Examinations

An adequate number of examinations is required to determine whether the visual field is progressing. A recommendation to perform six visual fields in the first 2 years in newly diagnosed has been made to quickly identify those patients with rapid progression [5]. Thereafter, the number of visual field examination depends on the age of the patient, stage of damage, and the rate of progression that has to be detected. In most patients, the visual field changes slowly and is influenced by variability that increases with increasing visual field damage.

Summary for the Clinician

- To avoid misinterpreting a visual field, attention should be paid to visual field quality (reliability, learning effects, etc.) and test artifacts (eyelid defects, lens rim defects, clover-leaf patterns, abnormal sensitivity).
- Statistical analyses provided by the visual field printout are a valuable complement to clinical evaluation and diagnosis.
- Many tests are usually required to determine whether a visual field is progressing in order to separate true change from variability.

References

1. Bengtsson B, Heijl A. A visual field index for calculation of glaucoma rate of progression. Am J Ophthalmol. 2008;145:343–53.
2. Bengtsson B, Lindgren A, Heijl A, Lindgren G, Asman P, Patella M. Perimetric probability maps to

separate change caused by glaucoma from that caused by cataract. Acta Ophthalmol Scand. 1997;75:184–8.
3. Lee JM, Cirineo N, Ramanathan M, et al. Performance of the visual field index in glaucoma patients with moderately advanced visual field loss. Am J Ophthalmol. 2014;157:39–43.
4. Rao HL, Senthil S, Choudhari NS, Mandal AK, Garudadri CS. Behavior of visual field index in advanced glaucoma. Invest Ophthalmol Vis Sci. 2013;54:307–12.
5. Chauhan BC, Garway-Heath DF, Goni FJ, et al. Practical recommendations for measuring rates of visual field change in glaucoma. Br J Ophthalmol. 2008;92:569–73.
6. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology. 1999;106:2144–53.
7. Chauhan BC, LeBlanc RP, Shaw AM, Chan AB, McCormick TA. Repeatable diffuse visual field loss in open-angle glaucoma. Ophthalmology. 1997;104:532–8.
8. Drance SM, Douglas GR, Airaksinen PJ, Schulzer M, Hitchings RA. Diffuse visual field loss in chronic open-angle and low-tension glaucoma. Am J Ophthalmol. 1987;104:577–80.
9. Henson DB, Artes PH, Chauhan BC. Diffuse loss of sensitivity in early glaucoma. Invest Ophthalmol Vis Sci. 1999;40:3147–51.
10. Artes PH, Nicolela MT, LeBlanc RP, Chauhan BC. Visual field progression in glaucoma: total versus pattern deviation analyses. Invest Ophthalmol Vis Sci. 2005;46:4600–6.

Other Tests in Glaucoma: Genetic Testing

18

Janey L. Wiggs

Core Messages

- Glaucoma genes have been identified for both adult-onset and early-onset forms of the disease.
- Current genetic tests are based on direct gene sequencing and are available for: Juvenile-onset open-angle glaucoma (MYOC); Axenfeld–Rieger syndrome and other types of anterior segment dysgenesis (FOXC1, PITX2, PAX6, LMX1B); congenital glaucoma (CYP1B1, LTBP2); and familial normal-tension glaucoma (OPTN, TBK1).
- Genetic testing is performed on a DNA sample from a patient.
- A number of CLIA-certified laboratories currently perform genetic testing for glaucoma genes.
- Glaucoma gene testing can help patients and their families understand their disease risk.
- Genetic counseling is an important part of genetic testing, as patients with mutations causing different forms of glaucoma have different risks of transmitting the disease to their offspring.
- Most glaucoma gene mutations cannot yet be correlated with specific disease outcomes; however, some phenotypes associated with some mutations in MYOC may help direct therapeutic decisions.

18.1 What Genetic Tests Are Currently Available to Test or Screen for Glaucoma?

One of the goals of human genetic research is to develop novel diagnostic and screening tests based on the identification of the genes responsible for the disease. Genes associated with adult-onset disease (primary open-angle glaucoma, angle-closure glaucoma, and exfoliation glaucoma) influence disease susceptibility, but are not necessarily causative. Mutations in genes responsible for early-onset forms of glaucoma cause disease. The AAO task force for genetic testing recommends offering genetic testing to patients with clinical findings suggestive of a Mendelian disorder whose causative gene(s) have been identified [1]. The genes known to cause early-onset glaucoma fit this criterion including: juvenile primary open-angle glaucoma (MYOC), familial normal-tension glaucoma

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(OPTN, TBK1), glaucoma associated with Axenfeld–Rieger syndrome and other anterior segment dysgenesis disorders (FOXC1, PITX2, PAX6, LMX1B), and congenital glaucoma (CYP1B1, LTBP2) [2].

Theoretically, a gene-based test is available for any glaucoma condition with a known causative gene. However, before a genetic test is useful it must meet the sensitivity and specificity expectations for screening or diagnostic tests. For glaucoma gene testing, the genes responsible for the early-onset forms of glaucoma, including anterior segment dysgenesis, are specific (i.e., a mutation accurately identifies the condition). The clinical sensitivity of the test is low because the current collection of genes only accounts for approximately 30 % of early-onset patients [3]; however, this situation will improve as new early-onset glaucoma genes are discovered. Genetic tests based on genes known to be associated with adult-onset glaucoma are neither specific nor sensitive at this time.

As disease-causing mutations may occur throughout the coding sequence of most genes, current tests are based on direct sequencing of genomic DNA from a biological sample collected from an affected patient. Sequencing may use the polymerase chain reaction (PCR), where each exon of the gene to be tested is selectively amplified and sequenced. Using next-generation sequencing all of the early-onset glaucoma genes can be tested for mutations at one time. This approach is preferred as many of the early-onset glaucoma genes can result in similar phenotypes. Additionally, the next-generation sequencing test is not affected by the variation in gene size, which can make testing larger genes more time consuming using traditional PCR-based sequencing. Once a mutation is identified in an affected individual, the remaining family members can be rapidly tested for the specific DNA sequence change regardless of the size of the gene.

18.1.1 Anterior Segment Dysgenesis

Four genes responsible for anterior segment dysgenesis syndromes, including Axenfeld–Rieger syndrome and Aniridia, have been identified: FOXC1, PITX2, PAX6, and in some cases of Nail Patella syndrome with glaucoma, LMX1B. Many disease-causing mutations have been identified in each of these genes in patients with abnormal development of the ocular anterior segment and glaucoma. Collectively PITX2 and FOXC1 mutations account for approximately 50 % of the cases of glaucoma associated with anterior segment dysgenesis [4]. In patients with Aniridia, over 80 % have identifiable mutations in PAX6 [5]. LMX1B mutations are a rare cause of glaucoma, but in patients with nail patella syndrome and glaucoma, mutations can be found in a majority of affected individuals [6]. All the anterior segment dysgenesis conditions exhibit considerable variable expressivity of the causative genetic defect, even within the same family. If a patient is found to carry a mutation in one of these genes, it is important to test all available family members, as some mutation carriers may be asymptomatic but may still pass severe disease onto their children (see genetic counseling below).

18.1.2 Juvenile-Onset Open-Angle Glaucoma

Up to 20 % of patients affected by open-angle glaucoma with age of onset before the age of 40 have mutations in MYOC, the gene coding for myocilin [7, 8]. MYOC has only three coding exons, and most of the mutations responsible for glaucoma are located in the third exon. If a patient with an early-onset form of glaucoma does not have an MYOC mutation, one could consider testing for mutations in the anterior segment gene panel (listed above) as the clinical features of the anterior segment syndromes can be minimal in some patients.

18.1.3 Congenital Glaucoma

Mutations in CYP1B1 have been identified in patients with congenital glaucoma throughout the world [9] and are especially likely in families with consanguinity [10]. Unlike juvenile open-angle glaucoma or the anterior segment dysgenesis syndromes that are inherited as autosomal dominant traits, patients with congenital glaucoma caused by mutations in CYP1B1 have an autosomal recessive inheritance pattern. Many different mutations have been described in this gene in patients with congenital glaucoma. The mutation carrier frequency in the United States has been estimated at 3.5 % [11]. Recently, mutations in LTBP2 have also been identified in patients with a diagnosis of congenital glaucoma [12]; however, the mutations in this gene also cause microspherophakia that may underlie the development of glaucoma [13].

18.1.4 Normal-Tension Glaucoma

The Optineurin E50K missense mutation (causing a change in the amino acid from a glutamate to a lysine at position 50 in the optineurin protein) in OPTN is a rare cause of familial low-tension glaucoma. In families that carry this mutation, there is an early onset (typically in the third or fourth decades) of severe optic nerve degeneration without significant elevation of intraocular pressure [14, 15]. Mutation of TBK1 can also cause familial normal-tension glaucoma [16]. Interestingly, TBK1 and OPTN interact and both participate in autophagy pathways [17].

18.1.5 Primary Open-Angle Glaucoma (Adult-Onset)

Mutations in the gene coding for myocilin (MYOC) affects 3–5 % of primary open-angle glaucoma (POAG) patients, where the onset is after the age of 40 [18]. Recent genome-wide association studies (GWAS) have identified a number of genes associated with POAG [19–23], but individually these associations do not have the specificity required for a gene-based diagnostic or screening test. The discovery of additional genes through further study could result in a comprehensive panel that may have the sensitivity and specificity required for a clinically useful genetic test for POAG.

18.1.6 Exfoliation Glaucoma

DNA sequence variants in genomic regions that contain the genes LOXL1 and CACNA1A have been found to be significantly associated with pseudoexfoliation glaucoma [24, 25]. The LOXL1 DNA sequence variants have a very high frequency in the affected population (98 %), but are also found in a significant percentage of individuals without disease (50 %). Thus, a test based on these results would have high sensitivity but low specificity, making it less useful, clinically. The CACNA1A variants are less common in both cases and controls.

Summary for the Clinician

- Genes contributing to various forms of glaucoma have been identified.
- Glaucoma genes that cause early-onset forms of glaucoma are appropriate targets for genetic testing.
- A good gene-based test has the same sensitivity and specificity expected for other types of clinical tests.
- Current genetic tests are based on direct gene sequencing and are available for: Juvenile-onset open-angle glaucoma (MYOC); Axenfeld–Rieger syndrome and other forms of anterior segment dysgenesis (FOXC1, PITX2, PAX6, LMX1B); congenital glaucoma (CYP1B1, LTBP2); familial normal-tension glaucoma (OPTN, TBK1).

18.2 Are Genetic Tests for Glaucoma of Practical Use in a Clinical Setting Today, or Are They More of Theoretical Use?

Currently, glaucoma genetic testing is most useful for families with early-onset forms of glaucoma [26]. Genetic testing may be useful in some cases of adult-onset primary open-angle glaucoma caused by mutations in MYOC. General guidelines for testing are described below.

18.2.1 Anterior Segment Dysgenesis

For patients affected with conditions causing abnormal development of the ocular anterior segment, genetic testing can be very useful, especially if other members of the patient's family are affected and the inheritance pattern is consistent with an autosomal dominant trait. As there is significant phenotype overlap between these conditions, one family member (typically the proband) is tested for mutations in all genes currently known to be associated with these syndromes (FOXC1, PITX2, PAX6, and LMX1B) as well as other early-onset glaucoma genes using next-generation sequencing. Once a gene defect is found in one member of the family, the entire family, both affected and unaffected members, should be screened. Given the well-documented variable expressivity of mutations in these genes, unaffected family members may actually be gene mutation carriers.

18.2.2 Juvenile-Onset Open-Angle Glaucoma

Families with autosomal dominant inheritance of early-onset glaucoma without evidence of anterior segment dysgenesis can be tested for mutations in MYOC, the gene coding for myocilin. Approximately 20 % of these families will have an MYOC mutation, which can be associated with severe glaucoma that typically requires surgical treatment [27].

18.2.3 Congenital Glaucoma

Patients with a family history consistent with autosomal recessive congenital glaucoma should be screened for mutations in CYP1B1 and LTBP2, especially if there is a family history of consanguinity. In small families, autosomal recessive traits may appear as isolated traits, so "sporadic" cases of congenital glaucoma should also be screened for mutations in this gene. If a mutation is found, all family members should be screened to detect individuals who may be unaffected carriers.

18.2.4 Normal-Tension Glaucoma

Genetic testing for mutations in OPTN (Optineurin) and TBK1 can be useful in patients with an onset of normal-tension glaucoma in the third or fourth decade, or in those with a family history of normal-tension glaucoma.

18.2.5 Primary Open-Angle Glaucoma (Adult-Onset)

Mutations in the gene coding for myocilin (MYOC) may be found in up to 3–5 % of patients with adult-onset primary open-angle glaucoma. Mutations are more likely to be found in patients with a strong family history of glaucoma (especially those with siblings as well as an affected parent) and in individuals who are affected somewhat earlier than the typical adult-onset primary open-angle glaucoma patient (fourth or fifth decades).

Summary for the Clinician

- Current glaucoma gene testing is most useful for the early-onset forms of the disease.
- Patients with anterior segment dysgenesis should be tested for all four genes associated with these syndromes ideally using next-generation sequencing.

- Juvenile open-angle glaucoma patients with a strong family history should be tested for mutations in MYOC.
- Patients with recessive or sporadic forms of congenital glaucoma should be tested for mutations in CYP1B1 or LTBP2, especially if there is a family history of consanguinity.
- Normal-tension glaucoma patients with a family history could be tested for the OPTN and TBK1 mutations.
- Patients with a strong family history adult-onset primary open-angle glaucoma may benefit from MYOC mutation screening.

18.3 How Do I Collect Samples and Where Do I Send Them for Analysis?

Genetic testing typically uses DNA samples purified from white blood cells or from buccal (cheek) cells collected using a mouthwash procedure (swish and spit) (Fig. 18.1) or a buccal swab (Fig. 18.2). A blood sample provides the most DNA; however, the swish and spit method and buccal swabs can provide sufficient DNA for most genetic tests and frequently are more convenient to obtain from the patient. The lab performing the testing will indicate the best collection procedure for the test they are performing, and they will provide detailed instructions for obtaining the sample.

Once a sample is obtained, the genetic test is performed by a special laboratory equipped to perform the test. Laboratories performing clinical genetic testing must be certified by a state agency according to the Clinical Laboratory Improvement Amendment of 1988 (CLIA). If a lab is not CLIA certified, it is not allowed to provide results to the clinician or to the patient. CLIA-certified laboratories return test results to the clinician who has ordered the test. It is the responsibility of the clinician to convey the results to the patient and provide the necessary genetic counseling.

There are a number of CLIA-certified laboratories that perform genetic testing for the genes listed in this chapter. A current list of laboratories is found at the website GeneTests (www.genetests.org).

Fig. 18.1 For the mouthwash collection, a small bottle of Scope mouthwash is used for two separate swishes of 30-s each. The contents of each swish are placed into one of the specimen cups

Fig. 18.2 The buccal swabs are used to vigorously scrape cheek cells from the buccal membrane for 10 s and then are returned to their containers

Summary for the Clinician

- Genetic testing is performed on a DNA sample from the patient.
- DNA may be prepared from a blood sample or a buccal cell sample (from a mouthwash procedure or buccal swab).
- Genetic tests are performed in a CLIA-certified laboratory.
- Genetic test reports are conveyed to the patient through the clinician.
- Laboratories that currently perform glaucoma gene testing may be found at the GeneTests website.

18.4 How Should the Results of Genetic Testing Be Interpreted for the Patient's Use?

Glaucoma gene testing can help patients and their family members understand their risk of disease. In addition to the identification of individuals at risk for the disease, mutation-specific clinical outcomes (genotype/phenotype correlations) can direct appropriate treatment.

18.4.1 Genetic Counseling

A major benefit of mutation testing is the identification of individuals at risk for the disease. Affected individuals need to know the risk of transmitting the disease to their offspring and the risk that their siblings or other family members may develop the disease. Unaffected individuals may learn that they are mutation carriers, which can influence their risk of developing the disease and their risk of transmitting the mutation to their offspring. Physicians, by virtue of their medical training, are qualified to discuss disease risk in the context of mutation testing with their patients; however, trained genetic counselors can also help with this process if necessary. Specific issues of disease risk for the forms of glaucoma that can currently be tested for are discussed below.

18.4.2 Anterior Segment Dysgenesis Syndromes

A major concern in families with disease caused by mutations in FOXC1, PITX2, PAX6, and LMX1B is the variable expression of the disease phenotype even within families with the same mutation. Mildly affected family mem-

bers who are mutation carriers are at risk of transmitting the mutation to their offspring who may then develop severe disease. As very little is understood about the variable expressivity of the phenotype, it is not currently possible to predict the severity of phenotype in the offspring of mutation carriers. Counseling can be difficult in these families because those members who are mutation carriers with mild disease need to understand that 50 % of their offspring can inherit the mutation and that their offspring may develop severe, rather than mild, disease.

18.4.3 Juvenile Open-Angle Glaucoma

Mutations in MYOC that cause juvenile-onset glaucoma are transmitted as an autosomal dominant trait. Individuals who carry mutations should be advised that 50 % of their offspring are at risk for developing severe glaucoma.

18.4.4 Congenital Glaucoma

For families with mutations in CYP1B1 or LTBP2, it is important to test all family members so that mutation carriers can be identified. These individuals need to be counseled that they have a 25 % risk of having an affected child if their mate is also a mutation carrier. Mutation testing should be offered to prospective mates. In families with a history of consanguinity, this risk may be higher.

18.4.5 Normal-Tension Glaucoma

If an OPTN or TBK1 mutation is identified in a family, mutation carriers should be advised that they have a 50 % chance of transmitting the mutation to their offspring. These individuals should be followed carefully for the development of optic nerve disease and visual field changes.

18.4.6 Primary Open-Angle Glaucoma (Adult-Onset)

If an MYOC mutation is found in a POAG family, they should be advised that affected members have a 50 % chance of transmitting the disease to offspring.

18.4.7 Genotype/Phenotype Correlations

Most of the mutations in genes currently known to contribute to glaucoma have not been correlated with specific clinical outcomes. However, several mutations in MYOC, the gene coding for myocilin, are known to be associated with severe disease, including the PRO370LEU (amino acid proline at protein position 370 changed to amino acid leucine) and TYR437HIS (tyrosine amino acid at protein position 437 replaced by amino acid histidine) mutations. Carriers of these mutations nearly always require surgery for control of intraocular pressure [27]. In addition, several mutations in MYOC have been shown to be more likely to cause mild disease, including the GLN368STOP (glutamine at protein position 368 replaced by a stop codon) mutation, which is the most common MYOC mutation [28]. Individuals with these mutations may be successfully treated with topical medications. Interestingly, one MYOC mutation, Thr377Met (threonine at protein position 377 replaced by amino acid methionine), is frequently associated with hearing loss [29].

Summary for the Clinician

- Glaucoma gene testing can help patients and their families understand their disease risk.
- Genetic counseling for patients and families affected by anterior segment dysgenesis syndromes needs to include an explanation of the variable expressivity of the disease phenotype in these patients.

- Juvenile open-angle glaucoma is inherited as an autosomal dominant trait and 50 % of the offspring of affected individuals are at risk of this disease.
- Congenital glaucoma caused by CYP1B1 or LTBP2 is inherited as an autosomal recessive trait and the risk of transmitting the disease is influenced by the carrier frequency and consanguinity.
- Normal-tension glaucoma caused by OPTN or TBK1 mutations is transmitted as an autosomal dominant trait.
- Adult-onset primary open-angle glaucoma caused by MYOC mutations is transmitted as an autosomal dominant trait.
- Some MYOC mutations are associated with severe disease while others are associated with mild disease making informed treatment regimens possible.

References

1. Stone EM, Aldave AJ, Drack AV, Maccumber MW, Sheffield VC, Traboulsi E, Weleber RG. Recommendations for genetic testing of inherited eye diseases: report of the American Academy of Ophthalmology task force on genetic testing. Ophthalmology. 2012;119(11):2408–10.
2. Fan BJ, Wiggs JL. Glaucoma: genes, phenotypes, and new directions for therapy. J Clin Invest. 2010; 120(9):3064–72.
3. Wang R, Wiggs JL. Common and rare genetic risk factors for glaucoma. Cold Spring Harb Perspect Med. 2014;4(12):a017244.
4. Libby RT, Gould DB, Anderson MG, John SW. Complex genetics of glaucoma susceptibility. Annu Rev Genomics Hum Genet. 2005;6:15–44.
5. Robinson DO, Howarth RJ, Williamson KA, Van Heyningen V, Beal SJ, Crolla JA. Genetic analysis of chromosome 11p13 and the PAX6 gene in a series of 125 cases referred with aniridia. Am J Med Genet A. 2008;146(5):558–69.
6. Mimiwati Z, Mackey DA, Craig JE, Mackinnon JR, Rait JL, Liebelt JE, Ayala-Lugo R, Vollrath D, Richards JE. Nail-patella syndrome and its association with glaucoma: a review of eight families. Br J Ophthalmol. 2006;90:1505–9.
7. Alward WL, Kwon YH, Khanna CL, Johnson AT, Hayreh SS, Zimmerman MB, Narkiewicz J, Andorf JL, Moore PA, Fingert JH, Sheffield VC, Stone EM. Variations in the myocilin gene in patients with open-angle glaucoma. Arch Ophthalmol. 2002;120:1189–97.
8. Wiggs JL, Allingham RR, Vollrath D, Jones KH, De La Paz M, Kern J, Patterson K, Babb VL, Del Bono EA, Broomer BW, Pericak-Vance MA, Haines JL. Prevalence of mutations in TIGR/Myocilin in patients with adult and juvenile primary open-angle glaucoma. Am J Hum Genet. 1998;63:1549–52.
9. Chakrabarti S, Kaur K, Kaur I, Mandal AK, Parikh RS, Thomas R, Majumder PP. Globally, CYP1B1 mutations in primary congenital glaucoma are strongly structured by geographic and haplotype backgrounds. Invest Ophthalmol Vis Sci. 2006;47:43–77.
10. Bejjani BA, Stockton DW, Lewis RA, Tomey KF, Dueker DK, Jabak M, Astle WF, Lupski JR. Multiple CYP1B1 mutations and incomplete penetrance in an inbred population segregating primary congenital glaucoma suggest frequent de novo events and a dominant modifier locus. Hum Mol Genet. 2000;9:367–74.
11. Wiggs JL, Langgurth AM, Allen KF. Carrier frequency of CYP1B1 mutations in the United States (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2014;112:94–102.
12. Ali M, McKibbin M, Booth A, Parry DA, Jain P, Riazuddin SA, Hejtmancik JF, Khan SN, Firasat S, Shires M, Gilmour DF, Towns K, Murphy AL, Azmanov D, Tournev I, Cherninkova S, Jafri H, Raashid Y, Toomes C, Craig J, Mackey DA, Kalaydjieva L, Riazuddin S, Inglehearn CF. Null mutations in LTBP2 cause primary congenital glaucoma. Am J Hum Genet. 2009;84(5):664–71.
13. Inoue T, Ohbayashi T, Fujikawa Y, Yoshida H, Akama TO, Noda K, Horiguchi M, Kameyama K, Hata Y, Takahashi K, Kusumoto K, Nakamura T. Latent TGF-β binding protein-2 is essential for the development of ciliary zonule microfibrils. Hum Mol Genet. 2014;23(21):5672–82.
14. Aung T, Rezaie T, Okada K, Viswanathan AC, Child AH, Brice G, Bhattacharya SS, Lehmann OJ, Sarfarazi M, Hitchings RA. Clinical features and course of patients with glaucoma with the E50K mutation in the optineurin gene. Invest Ophthalmol Vis Sci. 2005;46:2816–22.
15. Hauser MA, Sena DF, Flor J, Walter J, Auguste J, Larocque-Abramson K, Graham F, Delbono E, Haines JL, Pericak-Vance MA, Rand Allingham R, Wiggs JL. Distribution of optineurin sequence variations in an ethnically diverse population of low-tension glaucoma patients from the United States. J Glaucoma. 2006;15:358–63.
16. Ritch R, Darbro B, Menon G, Khanna CL, Solivan-Timpe F, Roos BR, Sarfarzi M, Kawase K, Yamamoto

T, Robin AL, Lotery AJ, Fingert JH. TBK1 gene duplication and normal-tension glaucoma. JAMA Ophthalmol. 2014;132(5):544–8.
17. Minegishi Y, Iejima D, Kobayashi H, Chi ZL, Kawase K, Yamamoto T, Seki T, Yuasa S, Fukuda K, Iwata T. Enhanced optineurin E50K-TBK1 interaction evokes protein insolubility and initiates familial primary open-angle glaucoma. Hum Mol Genet. 2013;22(17):3559–67.
18. Souzeau E, Glading J, Keane M, Ridge B, Zhou T, Burdon KP, Craig JE. Predictive genetic testing experience for myocilin primary open-angle glaucoma using the Australian and New Zealand Registry of Advanced Glaucoma. Genet Med. 2014;16(7):558–63.
19. Thorleifsson G, Walters GB, Hewitt AW, Masson G, Helgason A, DeWan A, Sigurdsson A, Jonasdottir A, Gudjonsson SA, Magnusson KP, Stefansson H, Lam DS, Tam PO, Gudmundsdottir GJ, Southgate L, Burdon KP, Gottfredsdottir MS, Aldred MA, Mitchell P, St Clair D, Collier DA, Tang N, Sveinsson O, Macgregor S, Martin NG, Cree AJ, Gibson J, Macleod A, Jacob A, Ennis S, Young TL, Chan JC, Karwatowski WS, Hammond CJ, Thordarson K, Zhang M, Wadelius C, Lotery AJ, Trembath RC, Pang CP, Hoh J, Craig JE, Kong A, Mackey DA, Jonasson F, Thorsteinsdottir U, Stefansson K. Common variants near CAV1 and CAV2 are associated with primary open-angle glaucoma. Nat Genet. 2010;42(10):906–9.
20. Burdon KP, Macgregor S, Hewitt AW, Sharma S, Chidlow G, Mills RA, Danoy P, Casson R, Viswanathan AC, Liu JZ, Landers J, Henders AK, Wood J, Souzeau E, Crawford A, Leo P, Wang JJ, Rochtchina E, Nyholt DR, Martin NG, Montgomery GW, Mitchell P, Brown MA, Mackey DA, Craig JE. Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. Nat Genet. 2011;43(6):574–8.
21. Wiggs JL, Yaspan BL, Hauser MA, Kang JH, Allingham RR, Olson LM, Abdrabou W, Fan BJ, Wang DY, Brodeur W, Budenz DL, Caprioli J, Crenshaw A, Crooks K, Delbono E, Doheny KF, Friedman DS, Gaasterland D, Gaasterland T, Laurie C, Lee RK, Lichter PR, Loomis S, Liu Y, Medeiros FA, McCarty C, Mirel D, Moroi SE, Musch DC, Realini A, Rozsa FW, Schuman JS, Scott K, Singh K, Stein JD, Trager EH, Vanveldhuisen P, Vollrath D, Wollstein G, Yoneyama S, Zhang K, Weinreb RN, Ernst J, Kellis M, Masuda T, Zack D, Richards JE, Pericak-Vance M, Pasquale LR, Haines JL. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. PLoS Genet. 2012;8(4):e1002654.
22. Gharahkhani P, Burdon KP, Fogarty R, Sharma S, Hewitt AW, Martin S, Law MH, Cremin K, Bailey JN, Loomis SJ, Pasquale LR, Haines JL, Hauser MA, Viswanathan AC, McGuffin P, Topouzis F, Foster PJ, Graham SL, Casson RJ, Chehade M, White AJ, Zhou T, Souzeau E, Landers J, Fitzgerald JT, Klebe S, Ruddle JB, Goldberg I, Healey PR; Wellcome Trust Case Control Consortium 2; NEIGHBORHOOD Consortium, Mills RA, Wang JJ, Montgomery GW, Martin NG, Radford-Smith G, Whiteman DC, Brown MA, Wiggs JL, Mackey DA, Mitchell P, MacGregor S, Craig JE. Common variants near ABCA1, AFAP1 and GMDS confer risk of primary open-angle glaucoma. Nat Genet. 2014;46(10):1120–5
23. Chen Y, Lin Y, Vithana EN, Jia L, Zuo X, Wong TY, Chen LJ, Zhu X, Tam PO, Gong B, Qian S, Li Z, Liu X, Mani B, Luo Q, Guzman C, Leung CK, Li X, Cao W, Yang Q, Tham CC, Cheng Y, Zhang X, Wang N, Aung T, Khor CC, Pang CP, Sun X, Yang Z. Common variants near ABCA1 and in PMM2 are associated with primary open-angle glaucoma. Nat Genet. 2014;46(10):1115–9.
24. Thorleifsson G, Magnusson KP, Sulem P, Walters GB, Gudbjartsson DF, Stefansson H, Jonsson T, Jonasdottir A, Jonasdottir A, Stefansdottir G, Masson G, Hardarson GA, Petursson H, Arnarsson A, Motallebipour M, Wallerman O, Wadelius C, Gulcher JR, Thorsteinsdottir U, Kong A, Jonasson F, Stefansson K. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science. 2007;317(5843):1397–400.
25. Aung T, Ozaki M, Mizoguchi T, Allingham RR, Li Z, Haripriya A, Nakano S, Uebe S, Harder JM, Chan AS, Lee MC, Burdon KP, Astakhov YS, Abu-Amero KK, Zenteno JC, Nilgün Y, Zarnowski T, Pakravan M, Safieh LA, Jia L, Wang YX, Williams S, Paoli D, Schlottmann PG, Huang L, Sim KS, Foo JN, Nakano M, Ikeda Y, Kumar RS, Ueno M, Manabe S, Hayashi K, Kazama S, Ideta R, Mori Y, Miyata K, Sugiyama K, Higashide T, Chihara E, Inoue K, Ishiko S, Yoshida A, Yanagi M, Kiuchi Y, Aihara M, Ohashi T, Sakurai T, Sugimoto T, Chuman H, Matsuda F, Yamashiro K, Gotoh N, Miyake M, Astakhov SY, Osman EA, Al-Obeidan SA, Owaidhah O, Al-Jasim L, Al Shahwan S, Fogarty RA, Leo P, Yetkin Y, Oğuz Ç, Kanavi MR, Beni AN, Yazdani S, Akopov EL, Toh KY, Howell GR, Orr AC, Goh Y, Meah WY, Peh SQ, Kosior-Jarecka E, Lukasik U, Krumbiegel M, Vithana EN, Wong TY, Liu Y, Koch AE, Challa P, Rautenbach RM, Mackey DA, Hewitt AW, Mitchell P, Wang JJ, Ziskind A, Carmichael T, Ramakrishnan R, Narendran K, Venkatesh R, Vijayan S, Zhao P, Chen X, Guadarrama-Vallejo D, Cheng CY, Perera SA, Husain R, Ho SL, Welge-Luessen UC, Mardin C, Schloetzer-Schrehardt U, Hillmer AM, Herms S, Moebus S, Nöthen MM, Weisschuh N, Shetty R, Ghosh A, Teo YY, Brown MA, Lischinsky I; Blue Mountains Eye Study GWAS Team; Wellcome Trust Case Control Consortium 2, Crowston JG, Coote M, Zhao B, Sang J, Zhang N, You Q, Vysochinskaya V, Founti P, Chatzikyriakidou A, Lambropoulos A, Anastasopoulos E, Coleman AL, Wilson MR, Rhee DJ, Kang JH, May-Bolchakova I, Heegaard S, Mori K, Alward WL, Jonas JB, Xu L, Liebmann JM, Chowbay B, Schaeffeler E, Schwab M, Lerner F,

Wang N, Yang Z, Frezzotti P, Kinoshita S, Fingert JH, Inatani M, Tashiro K, Reis A, Edward DP, Pasquale LR, Kubota T, Wiggs JL, Pasutto F, Topouzis F, Dubina M, Craig JE, Yoshimura N, Sundaresan P, John SW, Ritch R, Hauser MA, Khor CC. A common variant mapping to CACNA1A is associated with susceptibility to exfoliation syndrome. Nat Genet. 2015;47(4):387–92.

26. Wiggs JL, Pierce EA. Genetic testing for inherited eye disease: who benefits? JAMA Ophthalmol. 2013;131(10):1265–6.
27. Hewitt AW, Mackey DA, Craig JE. Myocilin allele-specific glaucoma phenotype database. Hum Mutat. 2008;29:207–11.
28. Allingham RR, Wiggs JL, De La Paz MA, et al. Gln368STOP myocilin mutation in families with late-onset primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 1998;39:2288–95.
29. Simm RM, Fingert JH, Craig JE, Mcnaught AI, Mackey DA. Normal range of hearing associated with myocilin Thr377Met. Ophthalmic Genet. 1999;20:205–7.

Other Tests in Glaucoma: Optic Nerve Blood Flow I

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Core Messages

- Current evidence does not support the suggestion that optic nerve blood flow should be routinely assessed in glaucoma patients.
- The methods currently available to measure blood flow generally assess aspects of hemodynamics that indirectly measure blood flow, thereby providing limited information in terms of direct quantitative outcome measures.
- Presently, there is no proven medical therapy to improve ocular blood flow other than modification of the existing systemic hypotensive medication.
- Reduction of Ocular blood flow secondary to lowering of perfusion pressure can predict the progression of glaucoma.
- Currently, there is limited evidence linking disease severity with reduced blood flow.

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19.1 Should Optic Nerve Blood Flow Be Measured in Glaucoma and Glaucoma Suspect Patients?

The body of evidence to date does not yet support the suggestion that blood flow in the optic nerve should be routinely measured in glaucoma and glaucoma suspect patients. This is primarily due to the fact that no single blood flow device at present can simultaneously evaluate all the vascular beds relevant to glaucoma [1]. Also, the currently available methods provide limited information on quantitative blood flow. They typically measure some surrogate parameters that are assumed to reflect volumetric perfusion, such as vessel diameter, pulsatility, and velocity of flow, or they extrapolate on change in blood flow as a result of a provocative test (including flicker stimulation, O_2 and CO_2 inhalation, and cold pressor tests). Therefore, the ideal test to measure comprehensive ocular blood flow (OBF) in the routine patient is yet to be developed [1–3].

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Despite being unable to quantitatively assess OBF, there is evidence that blood flow is reduced in glaucoma patients [4–8]. Reduced blood flow has been reported to occur in the optic nerve [5], retina [6], choroid [9], retro bulbar vessels [10], and even in the brain and peripheral vascular system of glaucoma patients [11]. However, at this time only a few centers worldwide can comprehensively examine blood flow in all of these anatomical sites. Patients with glaucoma generally do not have access to medical research centers offering comprehensive OBF assessment. Another problem is that the information obtained by these tests is not practically useful for the clinician as there are few *evidence-based treatments or guidelines* as to how to treat patients with reduced OBF.

Summary for the Clinician

- Except at a few research centers measurement of OBF is limited.
- There are currently no evidence-based treatments to improve OBF if it is proven to be pathological.
- Current methods of OBF measurement are indirect measures.
- Currently, routine measurement of OBF cannot be recommended.

19.2 Is Abnormal Ocular Blood Flow Causal in Glaucoma and Glaucoma Progression, and Does It Correlate with Disease Severity?

OBF can be disturbed in all anatomical locations of the glaucomatous eye [4–8]. Several published studies have shown that the reduction of OBF predicts the progression of glaucomatous neuropathic damage [10, 12, 13]. Recently, published prospective clinical studies suggest that vascular factors, such as perfusion pressure, are related to glaucoma progression [14, 15]. Finally, current reviews state that reduced perfusion pressure at the optic disc compromises OBF leading to glaucomatous damage [4–6].

Despite these facts, the etiology of reduced OBF and whether or not reduced OBF is causal for glaucomatous optic neuropathy is unknown [8]. It has been postulated by Grieshaber et al. that the link between glaucoma and OBF is actually due to an instability of OBF (vasospasm) that leads to recurrent reperfusion injury [8], rather than to a permanent reduction of flow. Damage likely occurs when a reduction of ocular perfusion pressure (OPP) exceeds the capacity of autoregulation to increase flow. With abnormal or absent autoregulation, a subtle reduction of OPP will reduce OBF. Interestingly, there is a component of OBF reduction that is independent of IOP and that precedes glaucomatous damage, especially in NTG patients and sometimes this reduction is not just confined to the eye [16–18].

Summary for the Clinician

- Reduced OBF and OPP have been associated with glaucoma and its progression.
- A causal relationship between OBF and glaucoma has not yet been established.
- Instability of OBF, due to derangements in vascular autoregulation, has been hypothesized to be a potential cause of glaucoma as well.

19.3 Which Glaucoma Patients May Suffer from Ocular Blood Flow Impairment?

The following glaucoma patients or glaucoma suspects may suffer from OBF disturbance: those with hypertension, hypotension, vasospasm, nocturnal blood pressure dips, and diabetes.

19.3.1 Patients with a History of Cardiovascular Diseases and Diabetes

19.3.1.1 Presence of Systemic Hypertension or Hypotension

While a number of studies have suggested that hypertension is a risk factor for open angle glaucoma (OAG) [19–22], others report a negative or no significant relationship between hypertension and glaucoma [14, 23, 24]. The Early Manifest Glaucoma Treatment Trial recently reported that early and untreated OAG patients with high baseline IOP and a self-reported cardiovascular disease history have close to a threefold chance of long-term progression of their glaucoma compared to patients without cardiovascular disease history [15].

Systemic hypertensive treatment may include beta blockers or calcium channel antagonists, both of which may alter optic nerve perfusion and interfere with the potential risk assessment of OAG. Beta blockers may induce vasoconstriction of peripheral vessels and cause reduced perfusion at the level of the optic nerve [25]. Calcium channel antagonists are peripheral vasodilators and theoretically may increase optic nerve perfusion, a possible beneficial effect for NTG and OAG patients [26, 27]. However, reports indicate that patients taking systemic calcium channel antagonists have a significantly increased risk of developing OAG [28]. The Rotterdam Eye Study recently reported that participants taking calcium channel antagonists for systemic hypertension had a 1.8-fold higher risk of developing incident OAG [29] than those not taking these medications. These results are in contradiction to other small studies ($n<60$ in each study) that support the use of calcium channel antagonists for the treatment of NTG [27, 30].

The Thessaloniki Eye Study [31] and a recent study by Jonas [32] showed that in persons without glaucoma, both lower diastolic blood pressure secondary to systemic antihypertensive and lower OPP were associated with increased optic nerve cupping and thinner neuroretinal rims, thus suggesting that hypotension or low OPP may predispose one to glaucoma. The Barbados Eye Study also recently reported that the lower the OPP the greater the risk to develop OAG, with the relative risk at least doubling in the lowest perfusion pressure categories [14]. These results are in line with a recent review by Pache and Flammer [7] who concluded that the evidence is stronger for a link between OAG and hypotension than between OAG and hypertension.

19.3.1.2 Patients with Vasospasm

Another potential source of glaucomatous optic nerve damage is a transient change in vascular perfusion due to vasospasm [11, 26]. Such vascular alterations may provoke reperfusion damage [33]. Vasospasm can be provoked by many factors, including exposure to cold, stress, emotional upset, and nicotine. These frequently encountered triggers may possibly promote daily episodes of hypoxia–reperfusion injury [7].

The data concerning an association between vasospasm and glaucoma is conflicting, however. Earlier reports suggested a link between vasospasm and NTG [34]. In NTG, migraine (a form of vasospasm) was reported to be an independent risk factor for progressive visual field loss [35]. These findings were not confirmed in high pressure POAG patients [36]. However, it has been suggested that POAG patients suffer from systemic autonomic and ocular vascular dysregulation. Cold provocation elicits blood pressure and OBF changes in patients with POAG which are different from that seen in control subjects [37]. Clinical features of primary vascular dysregulation include low blood pressure, slower onset of sleep and sleep apnea [38, 39], decreased awareness of thirst [40] coupled with low daily fluid intake, and low body mass index [8]. People with vasospastic syndrome usually are otherwise healthy and require no special treatment. Buckley et al. hypothesized that a possible cause of vasospastic syndrome is vascular endotheliopathy [41].

19.3.1.3 Patients with Nocturnal Blood Pressure Dips

Nocturnal hypoperfusion of the eye in glaucoma has been described widely by Hayreh et al. [42], who reported lower systolic and diastolic

nocturnal blood pressure in anterior ischemic optic neuropathy and in glaucomatous optic neuropathy. Other studies have also reported lower nocturnal blood pressure parameters in patients with progressive visual field defects compared to patients with stable visual fields [43] and in OAG patients with progression despite well-controlled IOP [44].

The most devastating factor in these patients is a drop in diastolic blood pressure to levels of 40 mmHg in contrast to values of 70 mmHg in normal patients. [42]. The literature suggests that nocturnal hypotension in the presence of other vascular risk factors may reduce optic nerve head blood perfusion below a critical level and thereby may play a role in the pathogenesis of glaucomatous optic neuropathy [45]. Ambulatory monitoring of blood pressure during a 24-h period is the method of choice to assess blood pressure dips.

19.3.1.4 Diabetes

The relationship between diabetes and OAG is also inconsistent. There was no association between diabetes, hypertension, and OAG in the prevalence papers from the Rotterdam Eye Study [19, 46]. Other studies have shown that diabetic patients are at significantly increased risk for developing POAG [47, 48].

19.3.2 Patients Who Progress despite Reaching Target IOP or with Fluctuating IOP and Pulse Pressure

Abnormal autoregulation of the optic nerve blood flow seems to occur in both NTG and progressive POAG patients despite a "normalized" IOP [33]. "Primary vascular dysregulation syndrome" is considered as a main cause of abnormal autoregulation by Grieshaber et al. [8]. It is hypothesized that autoregulation in this syndrome is not properly adapted to the local needs of various organs and tissues. The vascular systems of subjects with primary vascular dysregulation syndrome tend to respond differently to various stimuli than the normal patients.

In patients with untreated POAG, Sehi et al. demonstrated that the regions of the greatest diurnal change in rim topography had significant diurnal changes in capillary blood flow. These diurnal changes were not seen in normal subjects [49].

19.3.3 NTG Patients with Migraine and or Disc Hemorrhages

Normal tension glaucoma is much more common than was previously recognized. Population surveys reveal that 35–60 % of newly diagnosed patients with POAG have NTG [50]. NTG patients have a high incidence of disc hemorrhage [51]. Disc hemorrhage is considered to be a serious risk factor for the development and progression of optic disc damage in NTG as well as in POAG [7, 15, 52, 53]. Rasker et al. reported visual field deterioration in 80 % of NTG patients with disc hemorrhage compared to 14 % in ocular hypertension patients [54]. This finding is consistent with the OHTS study results [55]. Disc hemorrhages possibly represent impaired integrity of the vascular wall and therefore are considered a vascular risk factor in NTG.

Patients with NTG suffering from primary vascular dysregulation syndrome also suffer migraines more often than does the general population. Migraines were found to be a significant risk factor for glaucomatous optic neuropathy [56], as well as for progression in The Collaborative Normal Tension Glaucoma Study [57].

Summary for the Clinician

- OBF may be impaired in patients with cardiovascular disease, vasospasm, nocturnal hypotension, diabetes although much of the evidence is conflicting.
- Autonomic dysregulation is an attractive theory for patients whose glaucoma continues to progress despite low IOPs.
- Disc hemorrhages may represent a vascular risk factor for glaucoma.

19.4 What Are the Most Common Techniques to Measure Optic Nerve Blood Flow and What Are Their Limitations?

19.4.1 Color Doppler Imaging

Color Doppler Imaging (CDI) is a combination of ultrasound imaging with Doppler shift analysis. In the eye, it is typically used to assess hemodynamic parameters of the ophthalmic artery, central retinal artery, and posterior ciliary arteries. Two blood velocity values are measured by CDI: peak systolic velocity (PSV) and end diastolic velocity (EDV). The CDI unit calculates a resistive index (RI), which is expressed as RI = (PSV − EDV)/PSV. Based on studies of the brachial artery, the CDI provides RI data that is important for the quantification of downstream resistance [58]. However, it is unclear whether the RI represents a valid measure in terms of the retinal vasculature [59].

An important point to make about CDI is that it measures blood velocity and not blood flow. In related techniques such as transcranial Doppler (TCD) imaging, it can be assumed that a change in velocity accurately reflects changes in blood flow since the diameter of the larger cerebral vessels has been demonstrated to change minimally during provocation with hyperventilation [60]. In this situation, change in blood flow is thought to be governed by altered vascular resistance of the downstream arterioles. However, the smaller ocular vessels assessed by CDI have contractile capabilities, and therefore, any direct relationship between change in velocity and change in flow is invalid.

Another major problem with CDI is its limited resolution. Large vessels, such as the ophthalmic and central retinal artery, can be measured reliably but the information obtained from the smaller posterior ciliary arteries, which are abundant and tortuous, is less reliable. A further caveat is that CDI is not capable of measuring velocities slower than 1 cm/s, and due to this fact small vessels appear to have an absence of flow. Calculation of total blood flow with this instrument is therefore impossible. Finally, the interpretation of CDI results and the accurate estimation of blood flow velocity require correction for the angle of the probe relative to the measured blood vessels. This is especially problematic with small ocular vessels. Repeating a CDI test requires a skilled operator using a handheld probe at the correct angle to reproduce an earlier assessment.

19.4.2 Laser Doppler Flowmetry

In this technique, laser light is directed towards the vascularized tissue where there are no visible large vessels. What is actually being measured is the flux of red blood cells (RBCs) through the illuminated volume of the tissue. This is a relative value of blood flow since the measurement represents the product of velocity and volume. Since there are differences in scattering properties between individuals, due to vascular density and orientation, it is invalid to compare results between patients. However, reproducibility within an individual patient is considered to be high [61].

The technique is based on the scattering theory of light in a tissue that was formulated by Bonner and Nossal [62]. The technique assumes that the direction of light impinging on erythrocytes is completely random and therefore the mean velocity of the erythrocytes and the blood volume is measured using arbitrary units (AU) [63].

The Heidelberg Retinal Flow meter (HRF) is a Scanning Laser Doppler Flow meter (SLDF) that combines laser Doppler flowmetry (LDF) with scanning laser technology [64]. It provides a two-dimensional map of the perfusion within the retina and optic nerve head, and it measures blood flux through the capillary beds of these areas. The Doppler shift in the reflected light is analyzed to determine blood velocity in the volume of tissue sampled by the laser beam. In addition, the HRF performs signal analysis that is required for calculating blood flow. This calculation results in a display of blood velocity, volume, and flow through

the scanned area but all parameters are displayed in AU. A software algorithm, the automatic full field perfusion image analyzer (AFFPIA), which is an add-on to the original HRF software, can further improve the analysis of images. The AFFPIA software excludes the artifactual effect of eye movements and of Doppler shifts that are outside the valid measurement range of the photo detector (derived from relatively large diameter blood vessels) and determines blood flow in the capillary bed over the entire perfusion image. However, there can be problems in interpreting scanning LDF images because flow from the underlying choriocapillaris or deeper optic nerve head vessels may confound results.

19.4.3 Pulsatile Ocular Blood Flow

Pulsatile Ocular Blood Flow (POBF) quantifies the pulsatile portion of total OBF (i.e., retinal and choroidal blood flow) measured during systole. POBF represents the calculated change in ocular volume over time that is derived from pulsatile variation in IOP [65]. This method utilizes a pneumotonometer connected to a computer system to record the ocular pulse wave. Variations in IOP are also recorded and used to derive intraocular volume and blood volume changes using a preset equation. However, the calculation of POBF from the change in IOP is based upon a model eye assuming a standard ocular rigidity [66–68]. Additionally, this method is based on the assumptions that (a) the pulsatile ocular volume changes mainly reflect choroidal blood flow volume changes that are responsible for 90 % of the OBF in each cardiac cycle, (b) that no retrograde blood flow occurs, and (c) that the outflow of blood is nonpulsatile. A recent study reported that POBF determinations are influenced by the pulsatile components of both the choroidal and retinal vasculature [69]. Reduced POBF measurements were reported in studies on NTG and POAG patients [65, 70, 71]. An initial decrease followed by an increase in POBF has been documented in patients with diabetes who subsequently develop diabetic retinopathy [72–74].

19.4.4 Angiography

The passage of fluorescent dye in angiography is an effective way to topographically assess choroidal and retinal blood flow, as well as anatomical structures. The introduction of indocyanine green (ICG) in the last decade, in addition to fluorescein dye, has provided valuable information on the pathological conditions of the choroid and retina [75]. Due to the use of a near-infrared wavelength of light that penetrates well into the choroid, ICG has a better ability than fluorescein to examine choroidal vascular abnormalities and can be used to quantify flow in large choroidal vessels. ICG binds to plasma proteins, which prevents its leakage from choroidal vessels into surrounding tissues.

Most angiography-based approaches utilize the measurement of retinal arteriovenous passage time (time between first appearance of the dye in an artery and in the corresponding vein) [9] or mean retinal circulation time (the difference between venous and arterial time) as measures of retinal blood velocity. These methods use video angiography and scanning laser ophthalmoscopy [76, 77]. One limitation of these methods is their assumption that all the blood in an area is supplied by one artery and drained by a specific vein, a fact that is not true [67]. These methods require excellent image quality to assess hyper and hypofluorescent areas.

19.4.5 Canon Laser Blood Flowmeter

The quantitative measurement of blood flow, rather than just blood velocity, is technologically challenging. The Canon laser blood flowmeter (CLBF) is the only device currently available that can simultaneously measure centerline blood velocity (mm/s) using Doppler and vessel diameter (μm) using densitometry, in order to derive retinal blood flow (μL/min) in absolute units. With the average velocity (V_{mean}) over a pulse cycle and diameter (D), flow through the vessel can be calculated as $(V_{mean}) \times (60c\pi) \times (D/2)$ [2].

The CLBF is a quantitative, noninvasive laser Doppler flowmeter that utilizes bidirectional

laser Doppler velocimetry (BLDV), which provides an absolute measurement of blood velocity in the target vessel, irrespective of the angle between the vessel and incident laser beam. The Canon laser blood flowmeter also incorporates a vessel tracking system that employs a linear sensor to monitor the target vessel and maintain centration of the laser beam during the 2-s measurement window (velocity is continuously measured over this time). It subsequently calculates retinal blood flow assuming a circular vessel profile and Poiseuille flow with high reproducibility [78]. However, the technique can only be used to measure blood flow within the major retinal arterioles and venules (i.e., those with lumen diameter>60 μm), and it is not suitable for the measurement of optic nerve head blood flow. We have used the CLBF to measure retinal blood flow in normal patients [78] as well as patients with glaucoma [79] and diabetes [80–83].

Summary for the Clinician

- There are many different instruments that measure various parameters related to blood flow.

References

1. Schmetterer L, Garhofer G. How can blood flow be measured? Surv Ophthalmol. 2007;52 suppl 2:S134–8.
2. Cioffi GA. Three assumptions: ocular blood flow and glaucoma. J Glaucoma. 1998;7(5):299–300.
3. Rechtman E, Harris A, Kumar R, et al. An update on retinal circulation assessment technologies. Curr Eye Res. 2003;27(6):329–43.
4. Grieshaber MC, Flammer J. Blood flow in glaucoma. Curr Opin Ophthalmol. 2005;16(2):79–83.
5. Harris A, Rechtman E, Siesky B, et al. The role of optic nerve blood flow in the pathogenesis of glaucoma. Ophthalmol Clin North Am. 2005;18(3):345–53. v.
6. Flammer J, Orgul S, Costa VP, et al. The impact of ocular blood flow in glaucoma. Prog Retin Eye Res. 2002;21(4):359–93.
7. Pache M, Flammer J. A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma. Surv Ophthalmol. 2006;51(3):179–212.
8. Grieshaber MC, Mozaffarieh M, Flammer J. What is the link between vascular dysregulation and glaucoma? Surv Ophthalmol. 2007;52 suppl 2:S144–54.
9. Duijm HF, van den Berg TJ, Greve EL. Choroidal haemodynamics in glaucoma. Br J Ophthalmol. 1997;81(9):735–42.
10. Galassi F, Sodi A, Ucci F, et al. Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study. Arch Ophthalmol. 2003;121(12):1711–5.
11. Emre M, Orgul S, Gugleta K, Flammer J. Ocular blood flow alteration in glaucoma is related to systemic vascular dysregulation. Br J Ophthalmol. 2004;88(5):662–6.
12. Martinez A, Sanchez M. Predictive value of colour Doppler imaging in a prospective study of visual field progression in primary open-angle glaucoma. Acta Ophthalmol Scand. 2005;83(6):716–22.
13. Satilmis M, Orgul S, Doubler B, Flammer J. Rate of progression of glaucoma correlates with retrobulbar circulation and intraocular pressure. Am J Ophthalmol. 2003;135(5):664–9.
14. Leske MC, Wu SY, Hennis A, et al. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology. 2008;115(1):85–93.
15. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007;114(11):1965–72.
16. Nicolela MT, Drance SM, Rankin SJ, et al. Color Doppler imaging in patients with asymmetric glaucoma and unilateral visual field loss. Am J Ophthalmol. 1996;121(5):502–10.
17. Kaiser HJ, Schoetzau A, Stumpfig D, Flammer J. Blood-flow velocities of the extraocular vessels in patients with high-tension and normal-tension primary open-angle glaucoma. Am J Ophthalmol. 1997;123(3):320–7.
18. Gasser P, Flammer J. Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma. Am J Ophthalmol. 1991;111(5):585–8.
19. Dielemans I, Vingerling JR, Algra D, et al. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study. Ophthalmology. 1995;102(1):54–60.
20. Mitchell P, Lee AJ, Rochtchina E, Wang JJ. Open-angle glaucoma and systemic hypertension: the blue mountains eye study. J Glaucoma. 2004;13(4):319–26.
21. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. Ophthalmology. 2000;107(7):1287–93.
22. Tielsch JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. Arch Ophthalmol. 1995;113(2):216–21.
23. Leske MC, Wu SY, Nemesure B, Hennis A. Incident open-angle glaucoma and blood pressure. Arch Ophthalmol. 2002;120(7):954–9.

24. Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthalmol Vis Sci. 2003;44(9):3783–9.
25. Yu DY, Su EN, Cringle SJ, et al. Systemic and ocular vascular roles of the antiglaucoma agents beta-adrenergic antagonists and Ca2+ entry blockers. Surv Ophthalmol. 1999;43 suppl 1:S214–22.
26. Flammer J, Pache M, Resink T. Vasospasm, its role in the pathogenesis of diseases with particular reference to the eye. Prog Retin Eye Res. 2001;20(3):319–49.
27. Netland PA, Chaturvedi N, Dreyer EB. Calcium channel blockers in the management of low-tension and open-angle glaucoma. Am J Ophthalmol. 1993; 115(5):608–13.
28. Langman MJ, Lancashire RJ, Cheng KK, Stewart PM. Systemic hypertension and glaucoma: mechanisms in common and co-occurrence. Br J Ophthalmol. 2005;89(8):960–3.
29. Muskens RP, de Voogd S, Wolfs RC, et al. Systemic antihypertensive medication and incident open-angle glaucoma. Ophthalmology. 2007;114(12):2221–6.
30. Kitazawa Y, Shirai H, Go FJ. The effect of Ca2(+) -antagonist on visual field in low-tension glaucoma. Graefes Arch Clin Exp Ophthalmol. 1989;227(5): 408–12.
31. Topouzis F, Coleman AL, Harris A, et al. Association of blood pressure status with the optic disk structure in non-glaucoma subjects: the Thessaloniki eye study. Am J Ophthalmol. 2006;142(1):60–7.
32. Jonas JB. Association of blood pressure status with the optic disk structure. Am J Ophthalmol. 2006;142(1):144–5.
33. Gherghel D, Orgul S, Gugleta K, et al. Relationship between ocular perfusion pressure and retrobulbar blood flow in patients with glaucoma with progressive damage. Am J Ophthalmol. 2000;130(5):597–605.
34. Broadway DC, Drance SM. Glaucoma and vasospasm. Br J Ophthalmol. 1998;82(8):862–70.
35. Delaney Y, Walshe TE, O'Brien C. Vasospasm in glaucoma: clinical and laboratory aspects. Optom Vis Sci. 2006;83(7):406–14.
36. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121(1):48–56.
37. Gherghel D, Hosking SL, Cunliffe IA. Abnormal systemic and ocular vascular response to temperature provocation in primary open-angle glaucoma patients: a case for autonomic failure? Invest Ophthalmol Vis Sci. 2004;45(10):3546–54.
38. Mojon DS, Hess CW, Goldblum D, et al. High prevalence of glaucoma in patients with sleep apnea syndrome. Ophthalmology. 1999;106(5):1009–12.
39. Karakucuk S, Goktas S, Aksu M, et al. Ocular blood flow in patients with obstructive sleep apnea syndrome (OSAS). Graefes Arch Clin Exp Ophthalmol. 2008;246(1):129–34.
40. Teuchner B, Orgul S, Ulmer H, et al. Reduced thirst in patients with a vasospastic syndrome. Acta Ophthalmol Scand. 2004;82(6):738–40.
41. Buckley C, Hadoke PW, Henry E, O'Brien C. Systemic vascular endothelial cell dysfunction in normal pressure glaucoma. Br J Ophthalmol. 2002; 86(2):227–32.
42. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WL. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. Am J Ophthalmol. 1994;117(5):603–24.
43. Graham SL, Drance SM, Wijsman K, et al. Ambulatory blood pressure monitoring in glaucoma. The nocturnal dip. Ophthalmology. 1995;102(1): 61–9.
44. Kaiser HJ, Flammer J, Graf T, Stumpfig D. Systemic blood pressure in glaucoma patients. Graefes Arch Clin Exp Ophthalmol. 1993;231(12):677–80.
45. Hayreh SS. Factors influencing blood flow in the optic nerve head. J Glaucoma. 1997;6(6):412–25.
46. de Voogd S, Ikram MK, Wolfs RC, et al. Is diabetes mellitus a risk factor for open-angle glaucoma? The Rotterdam Study. Ophthalmology. 2006;113(10): 1827–31.
47. Pasquale LR, Kang JH, Manson JE, et al. Prospective study of type 2 diabetes mellitus and risk of primary open-angle glaucoma in women. Ophthalmology. 2006;113(7):1081–6.
48. Bonovas S, Peponis V, Filioussi K. Diabetes mellitus as a risk factor for primary open-angle glaucoma: a meta-analysis. Diabet Med. 2004;21(6):609–14.
49. Sehi M, Flanagan JG, Zeng L, et al. Anterior optic nerve capillary blood flow response to diurnal variation of mean ocular perfusion pressure in early untreated primary open-angle glaucoma. Invest Ophthalmol Vis Sci. 2005;46(12):4581–7.
50. Shiose Y, Kitazawa Y, Tsukahara S, et al. Epidemiology of glaucoma in Japan—a nationwide glaucoma survey. Jpn J Ophthalmol. 1991;35(2): 133–55.
51. Kitazawa Y, Shirato S, Yamamoto T. Optic disc hemorrhage in low-tension glaucoma. Ophthalmology. 1986;93(6):853–7.
52. Drance SM, Fairclough M, Butler DM, Kottler MS. The importance of disc hemorrhage in the prognosis of chronic open angle glaucoma. Arch Ophthalmol. 1977;95(2):226–8.
53. Siegner SW, Netland PA. Optic disc hemorrhages and progression of glaucoma. Ophthalmology. 1996; 103(7):1014–24.
54. Rasker MT, van den Enden A, Bakker D, Hoyng PF. Deterioration of visual fields in patients with glaucoma with and without optic disc hemorrhages. Arch Ophthalmol. 1997;115(10):1257–62.
55. Budenz DL, Anderson DR, Feuer WJ, et al. Detection and prognostic significance of optic disc hemorrhages during the Ocular Hypertension Treatment Study. Ophthalmology. 2006;113(12):2137–43.

56. Phelps CD, Corbett JJ. Migraine and low-tension glaucoma. A case-control study. Invest Ophthalmol Vis Sci. 1985;26(8):1105–8.
57. Drance S, Anderson DR, Schulzer M. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol. 2001;131(6): 699–708.
58. Legarth J, Nolsoe C. Doppler blood velocity waveforms and the relation to peripheral resistance in the brachial artery. J Ultrasound Med. 1990;9(8): 449–53.
59. Polska E, Kircher K, Ehrlich P, et al. RI in central retinal artery as assessed by CDI does not correspond to retinal vascular resistance. Am J Physiol Heart Circ Physiol. 2001;280(4):H1442–7.
60. Valdueza JM, Balzer JO, Villringer A, et al. Changes in blood flow velocity and diameter of the middle cerebral artery during hyperventilation: assessment with MR and transcranial Doppler sonography. AJNR Am J Neuroradiol. 1997;18(10):1929–34.
61. Polska E, Polak K, Luksch A, et al. Twelve hour reproducibility of choroidal blood flow parameters in healthy subjects. Br J Ophthalmol. 2004;88(4):533–7.
62. Bonner RF, Nossal R. Principles of laser-Doppler flowmetry. In: Shepard AP, Oberg PA, editors. Laser-Doppler blood flowmetry. Boston, MD: Kluwer; 1990.
63. Petrig BL, Riva CE, Hayreh SS. Laser Doppler flowmetry and optic nerve head blood flow. Am J Ophthalmol. 1999;127(4):413–25.
64. Michelson G, Langhans MJ, Groh MJ. Perfusion of the juxtapapillary retina and the neuroretinal rim area in primary open angle glaucoma. J Glaucoma. 1996; 5(2):91–8.
65. Kerr J, Nelson P, O'Brien C. Pulsatile ocular blood flow in primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol. 2003;136(6):1106–13.
66. Silver DM, Farrell RA, Langham ME, et al. Estimation of pulsatile ocular blood flow from intraocular pressure. Acta Ophthalmol Suppl. 1989;191:25–9.
67. Silver DM, Farrell RA. Validity of pulsatile ocular blood flow measurements. Surv Ophthalmol. 1994;38(suppl):S72–80.
68. Silver DM, Geyer O. Pressure-volume relation for the living human eye. Curr Eye Res. 2000;20(2):115–20.
69. Zion IB, Harris A, Siesky B, et al. Pulsatile ocular blood flow: relationship with flow velocities in vessels supplying the retina and choroid. Br J Ophthalmol. 2007;91(7):882–4.
70. Fontana L, Poinoosawmy D, Bunce CV, et al. Pulsatile ocular blood flow investigation in asymmetric normal tension glaucoma and normal subjects. Br J Ophthalmol. 1998;82(7):731–6.
71. Aydin A, Wollstein G, Price LL, Schuman JS. Evaluating pulsatile ocular blood flow analysis in normal and treated glaucomatous eyes. Am J Ophthalmol. 2003;136(3):448–53.
72. Geyer O, Neudorfer M, Snir T, et al. Pulsatile ocular blood flow in diabetic retinopathy. Acta Ophthalmol Scand. 1999;77(5):522–5.
73. Savage HI, Hendrix JW, Peterson DC, et al. Differences in pulsatile ocular blood flow among three classifications of diabetic retinopathy. Invest Ophthalmol Vis Sci. 2004;45(12):4504–9.
74. MacKinnon JR, O'Brien C, Swa K, et al. Pulsatile ocular blood flow in untreated diabetic retinopathy. Acta Ophthalmol Scand. 1997;75(6):661–4.
75. Flower RW. Extraction of choriocapillaris hemodynamic data from ICG fluorescence angiograms. Invest Ophthalmol Vis Sci. 1993;34(9):2720–9.
76. Tanaka T, Muraoka K, Shimizu K. Fluorescein fundus angiography with scanning laser ophthalmoscope. Visibility of leukocytes and platelets in perifoveal capillaries. Ophthalmology. 1991;98(12):1824–9.
77. Wolf S, Arend O, Toonen H, et al. Retinal capillary blood flow measurement with a scanning laser ophthalmoscope. Preliminary results. Ophthalmology. 1991;98(6):996–1000.
78. Guan K, Hudson C, Flanagan JG. Variability and repeatability of retinal blood flow measurements using the Canon Laser Blood Flowmeter. Microvasc Res. 2003;65(3):145–51.
79. Venkataraman ST, Hudson C, Fisher JA, Rachmiel R, Ahmed T, Buys Y, Trope G, Flanagan JG. Retinal arteriolar and capillary response to isoxic hypercapnia in primary open angle glaucoma pre- & post-treatment. Singapore: World Glaucoma Congress; 2007.
80. Gilmore ED, Hudson C, Nrusimhadevara RK, et al. Retinal arteriolar hemodynamic response to an acute hyperglycemic provocation in early and sight-threatening diabetic retinopathy. Microvasc Res. 2007;73(3):191–7.
81. Gilmore ED, Hudson C, Nrusimhadevara RK, et al. Retinal arteriolar hemodynamic response to a combined isocapnic hyperoxia and glucose provocation in early sight-threatening diabetic retinopathy. Invest Ophthalmol Vis Sci. 2008;49(2):699–705.
82. Guan K, Hudson C, Wong T, et al. Retinal hemodynamics in early diabetic macular edema. Diabetes. 2006;55(3):813–8.
83. Gilmore ED, Hudson C, Nrusimhadevara RK, et al. Retinal arteriolar diameter, blood velocity, and blood flow response to an isocapnic hyperoxic provocation in early sight-threatening diabetic retinopathy. Invest Ophthalmol Vis Sci. 2007;48(4):1744–50.

Other Tests in Glaucoma: Optic Nerve Blood Flow II

20

Alon Harris and Brent Siesky

Core Messages

- Many population-based studies have found low ocular perfusion pressure to be an independent risk factor for open-angle glaucoma (OAG).
- During the last two decades, ocular hemodynamic assessment has evolved from a subjective description of visible vessels to direct quantitative measurement of blood-flow parameters.
- No single examination technique adequately assesses all relevant ocular vascular beds simultaneously or separately.
- A majority of the techniques for examining optic nerve hemodynamics are currently available only for research purposes.
- Patients with both normal and high tension OAG have been found to manifest ocular vascular abnormalities within different vascular beds of the eye and optic nerve.

20.1 What Evidence Is There that Vascular Alterations Play a Role in Open-Angle Glaucoma?

One-third of patients with primary OAG have normal intraocular pressures (IOPs) at the time of glaucoma diagnosis. This suggests that other risk factors, such as vascular changes, contribute to the pathogenesis of glaucomatous optic neuropathy [1, 2]. Many population-based studies, including the Barbados Eye Study, Proyecto VER (vision evaluation and research), Baltimore Eye Survey, and Egna-Neumarkt Glaucoma Study, have shown that reduced ocular perfusion pressure, and most often diastolic perfusion pressure, is a significant risk factor for the prevalence and incidence of OAG [3–6]. The Early Manifest Glaucoma Trial (EMGT) found that lower systolic perfusion pressure, lower systolic blood pressure, and cardiovascular disease history are

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predictors for glaucoma progression, strengthening the evidence for the role of vasculopathy in glaucoma [7]. While the association of ocular vasculature to OAG is apparent, debate remains regarding whether blood-flow abnormalities are primary insults, secondary to IOP-induced cellular damage, or a combination of vascular dysregulation and IOP synergistically contributing to OAG.

Summary for the Clinician

- Up to one-third of cases of OAG have normal IOP at diagnosis.
- Low ocular perfusion pressure has been found to be an independent risk factor for the development of OAG.
- The EMGT found low systolic perfusion pressure to be a risk factor for OAG progression.
- These findings support the role of optic nerve ischemia in the pathogenesis of OAG.

20.2 What Are the Positives and Negatives of Measuring Optic Nerve Blood Flow?

Assessment of a glaucoma patient's ocular vascular beds and optic nerve perfusion may provide important information to the clinician. The anatomical regions of particular interest in glaucoma include the capillary plexus of the superficial retinal nerve fiber layer, the pre- and intra-laminar optic nerve head, and the peripapillary choroid [8], as ocular blood-flow abnormalities have been reported in the optic nerve head, retinal, choroidal, and retrobulbar vasculatures. In the last two decades, ocular hemodynamic assessment has evolved from a subjective description of the visible vessels to direct quantitative measurement of blood-flow parameters, such as flow velocity, resistance to flow, circulation time, and most recently oxygen content of retinal blood vessels. It is important to acknowledge that no single imaging technology can assess all OAG-relevant vascular beds. Each technology evaluates specific locations and examines different aspects of ocular hemodynamics. Currently, it is not possible to directly assess and specifically treat a region in which there is abnormal blood flow and/or metabolism. Although the need to use multiple technologies with skilled technicians limits their comprehensive use in the clinical setting, various imaging modalities (discussed below) provide important insights which may assist clinicians in better understanding the contributing pathophysiological factors in OAG.

Summary for the Clinician

- Abnormal ocular blood flow has been confirmed in glaucoma patients.
- No single imaging technology can study all ocular vascular beds.
- Most technologies, which measure different aspects of optic nerve hemodynamics, are currently confined to research due to cost, expertise, and time required for analysis.

20.3 What Technologies Are Available to Measure Ocular Blood Flow?

There are various technologies used for measuring ocular hemodynamics [8]:

20.3.1 Color Doppler Imaging

Color Doppler Imaging (CDI) is widely used in many aspects of medicine including assessment of blood vessel flow velocities and resistance. Within the eye, CDI is often used to measure the ophthalmic, central retinal, and short posterior ciliary arteries' blood-flow velocities and calculates a resistive index (i.e., resistance to flow) in these vessels. Since most CDI methodologies do not measure vessel diameter, calculation of the absolute flow volume is often limited [9].

20.3.2 Heidelberg Retinal Flowmeter

This laser Doppler flowmeter is a confocal scanning laser that maps blood flow in retinal capillaries (Fig. 20.1). Several software methods for analysis have been used, including a pixel-by-pixel analysis method that provides blood flow, volume, and velocity data at the 25th, 50th, 75th, and 90th percentiles, combined with the percentage of zero-flow pixels, and corresponding total retinal capillary blood flow [10]. HRF allows for the study of red blood cell movement in the capillary network of the anterior optic nerve head and the peripapillary region.

20.3.3 Canon Laser Blood Flowmetry

The Canon laser blood flowmeter (CLBF) is a modified fundus camera equipped with two lasers: one measuring blood velocity by means of laser Doppler velocimetry and the other simultaneously measuring vessel diameter while tracking its location. This allows calculation of the retinal blood flow (μL/min) in the selected vessels [11, 12].

20.3.4 Laser Doppler Flowmetry

The laser Doppler flowmeter (LDF) is a laser Doppler device consisting of a modified fundus camera and computer. The LDF measures real-time blood cell perfusion in the capillary beds of retinal and choroidal tissue. It is used to measure choroidal blood flow in the foveal avascular zone and optic nerve head blood flow [13, 14].

20.3.5 Retinal Vessel Analyzer

The retinal vessel analyzer (RVA) was developed to produce real-time measurements of large retinal vessels with a spatial resolution less than 1 μm. This is accomplished by averaging hundreds of individual measurements acquired at a rate of 250/s. The RVA monitors

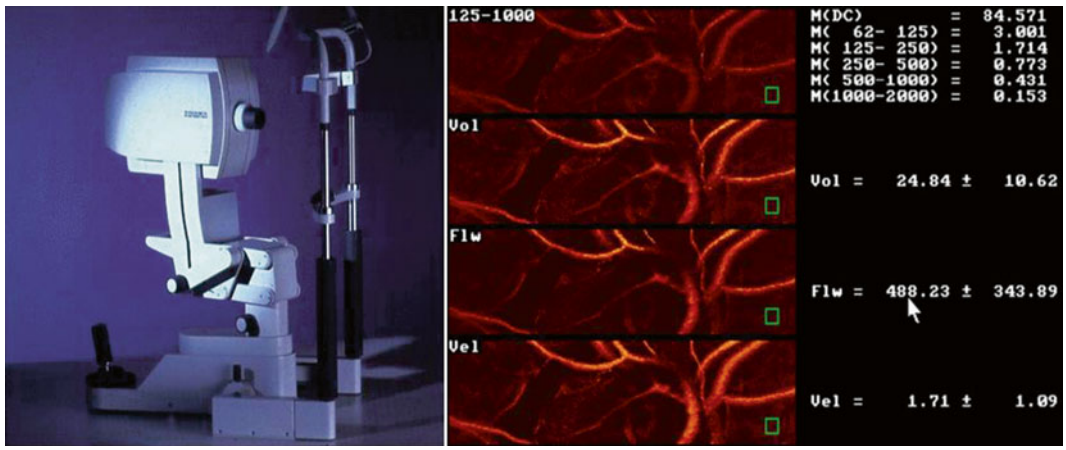

Fig. 20.1 Confocal scanning laser Doppler flowmetry (Heidelberg retinal flowmeter) of optic nerve head and peripapillary retina. The *left* picture: Heidelberg retinal flowmeter. The patient places his chin on the chinrest and his forehead against the bar. The technician aligns the laser with the pupil, which does not need to be dilated. The *right* picture: A conventional 10 × 10 pixel measurement window is positioned in an area without large vessels to collect the flow values in arbitrary units from the retina

the pulsation of retinal vessels throughout the cardiac cycle, but without measuring actual ocular blood flow [15].

20.3.6 Scanning Laser Ophthalmoscope

Scanning Laser Ophthalmoscope (SLO) fluorescein angiography (FA) evaluates passage of blood through the retinal vasculature. Retinal hemodynamics are quantified by arteriovenous passage (AVP) time and capillary transit velocities [16]. SLO indocyanine green (ICG) angiography provides a semiquantitive measure of the choroidal blood flow that perfuses the outer retinal layers and most of the optic nerve head [17]. These techniques can be invasive and costly.

20.3.7 Pulsatile Ocular Blood Flowmeter/Pascal Dynamic Contour Tonometer

Pulsatile Ocular Blood Flowmeter (POBF) and Pascal Dynamic Contour Tonometer (DCT) measure ocular pulse amplitude (OPA) [18, 19]. OPA is determined by the continuous recordings of the change in IOP resulting from variations in ocular volume with each pulse of blood within the eye producing an ocular pressure pulse wave and is presumed to correspond to pulsatile choroidal blood flow, although no direct measurements of blood flow or vasculature are obtained.

20.3.8 Fourier Domain Doppler Optical Coherence Tomography

Fourier Domain Doppler Optical Coherence Tomography (FD-OCT) combines the structural measurements of OCT with the retinal blood-flow measurements of laser Doppler in a single device. It is possible to capture high resolution Doppler information from retinal vessels in three dimensions [20, 21]. Retinal blood-flow scans (Fig. 20.2) transect all retinal branch arteries and veins that emerge from the ON, providing the basis for total retinal blood-flow measurement. An advantage to this technology is that blood flow can be measured as an absolute value (μL/min).

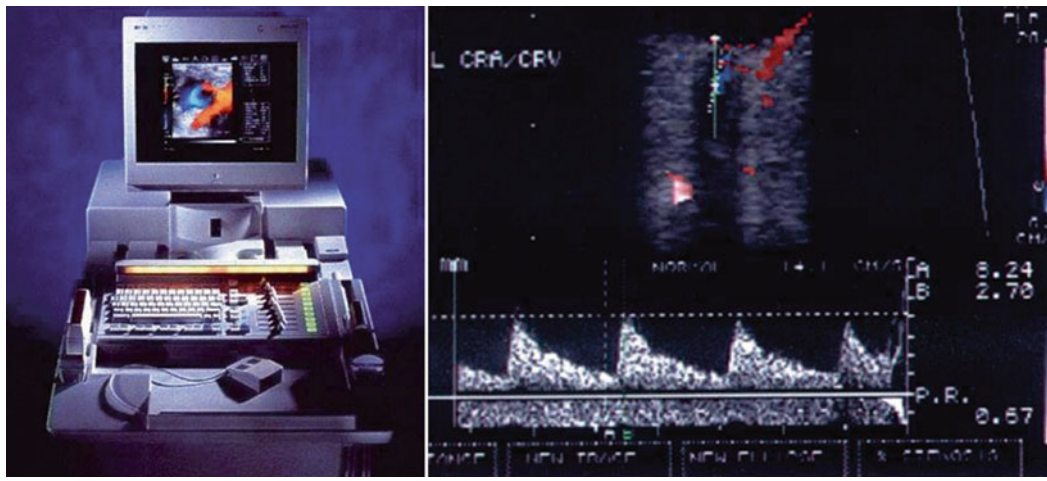

Fig. 20.2 Color Doppler imaging. The *left* picture: A color Doppler machine. The patient is seated comfortably in a half supine position. An ultrasound probe is placed on the closed eyelid and the optic nerve shadow is identified. The vessels sampled include the ophthalmic artery, central retinal artery, and the nasal and temporal short posterior ciliary arteries. The *right* picture: A color Doppler image of the central retinal artery and vein taken with a 7.5 MHz linear probe. The Doppler-shifted spectrum (time velocity curve) is displayed at the *bottom* of the image. The *red* and *blue* pixels represent blood-flow movement towards and away from the transducer, respectively

20.3.9 Retinal Oximetry

Methods of direct measurement of tissue oxygenation are a step toward revealing the impact of ischemia on retinal photoreceptor ganglion cells. The methodology of photographic retinal oximetry provides a more direct way to measure tissue oxygenation and metabolism. Retinal oximetry uses a modified fundus camera or similar device and developed algorithms to measure oxygen saturation in the arteries and veins, the difference of which is informative about tissue oxygenation and metabolism [22].

Summary for the Clinician

- CDI uses widely available ultrasound imaging devices to measure ophthalmic, central retinal, and short posterior ciliary arteries' blood-flow velocities (cm/s) and to calculate their resistance to flow.
- Heidelberg retinal flowmeter (HRF) uses a confocal scanning laser to map blood flow in retinal capillaries and provides measurements in arbitrary units.
- Newly emerging imaging modalities including FD-OCT and Retinal Oximetry are providing additional insights into OAG pathophysiology including parallel ocular structure and flow assessment and retinal tissue metabolism evaluations.

20.4 Are There Examples of Ocular Hemodynamic Abnormalities Found in OAG Patients?

20.4.1 Color Doppler Imaging

Rankin et al. found that OAG patients have reduced flow velocity and increased resistance to flow in the ophthalmic, central retinal, and short posterior ciliary arteries compared to controls [23]. In a 7-year prospective study, Galassi et al. demonstrated that OAG patients with progressing visual field changes have lower diastolic flow velocities and higher resistive indices in the ophthalmic artery than patients with stable visual fields [24] (Fig. 20.2).

20.4.2 Heidelberg Retinal Flowmeter

Michelson et al. found OAG patients had lower juxtapapillary retinal blood flow and neuroretinal rim area blood flow compared to age-matched healthy controls [25]. Sato et al. showed that blood-flow reductions in the neuroretinal rim correspond to regional visual field defects in eyes with normal-tension glaucoma [26].

20.4.3 Canon Laser Blood Flowmetry

Feke et al. found significant differences in blood flow in response to postural changes between primary OAG patients and controls, suggesting underlying autoregulatory dysfunction in glaucoma patients [27].

20.4.4 Laser Doppler Flowmetry

Boehm et al. found decreased blood flow in the temporal neuroretinal rim compared to nasal blood flow in healthy subjects, suggesting potential vulnerability of the temporal neuroretinal rim to ischemic insult [28].

20.4.5 Retinal Vessel Analyzer

Nagel et al. demonstrated that retinal vein diameter autoregulatory response to acute IOP elevation is diminished in patients with primary OAG [29]. Garhofer et al. found the autoregulatory response to flicker-induced vasodilation of retinal veins is significantly diminished in patients with glaucoma compared with healthy volunteers [30].

20.4.6 FA-Scanning Laser Ophthalmoscopy

Harris et al. showed that OAG patients had fluorescein filling defects in the superficial part of the optic disc and choroid, delayed arm-to-retina and retinal arterial and venous filling times, prolonged AVP time, and reduced velocity in the retinal circulation compared to controls [31, 32]. The AVP time correlated significantly with the optic nerve head size, visual field global indices, mean deviation, pattern standard deviation and corrected pattern standard deviation, and contrast sensitivity in normal-tension glaucoma patients [33].

20.4.7 ICG-Scanning Laser Ophthalmoscopy

Marengo et al. found that subjects with advanced glaucoma show prominent increase in the cup/disc area ratio, as well as marked capillary dropout [34]. O'Brart et al. demonstrated areas of hypofluorescence in the peripapillary region in late-phase angiograms in 68 % of glaucomatous eyes compared with 20 % of control eyes [35].

20.4.8 Pulsatile Ocular Blood Flowmeter/Pascal DCT

James et al. showed reduced OPA and pulsatile ocular blood flow in high and normal-pressure glaucoma [36]. von Schulthess et al. suggested that an early drop of more than 2.0 mmHg in OPA after trabeculectomy may be a good prognostic parameter for successful long-term control of IOP [37].

20.4.9 Fourier Domain Doppler Optical Coherence Tomography (FD-OCT)

Wang et al. showed that Doppler OCT retinal blood-flow measurements in glaucoma patients had significantly decreased retinal blood flow compared with normal eyes and excellent correlation with visual field and clinical presentations [38].

20.4.10 Retinal Oximetry

Olafsdottir et al. found advanced glaucoma patients have higher oxygen saturation in venules and lower arteriovenous difference in oxygen saturation compared with healthy individuals. The decreased arteriovenous difference in severe glaucoma may be related to lower oxygen consumption secondary to neuropathy [39]. Currently, more research is required to fully understand the potential and limitations of retinal oximetry [40].

Summary for the Clinician

- Patients with normal and high tension OAG have been found to have vascular abnormalities in the retinal, choroidal, and retrobulbar circulations.
- Autoregulatory dysfunction and metabolism defects have been reported in OAG patients.

20.5 How Are the Results of Blood-Flow Measuring Devices Interpreted and Are There Limitations to These Blood-Flow Imaging Techniques?

Since all the above techniques provide us with quantitative hemodynamic data but not with the absolute flow, it is necessary to evaluate their results with caution. Currently, most of these techniques are not used in the clinic and are primarily used for research purposes.

20.5.1 Color Doppler Imaging

Parallel changes in CDI peak systolic and end diastolic velocities may be interpreted as changes

in volumetric blood flow in the same direction [41]. Conversely, an increase in the peak systolic velocity may be interpreted as only proximal arterial stenosis. An increase in resistive index may reflect arterial stenosis distal to the point of measurement. Increased resistive index in the central retinal and short posterior ciliary arteries, without an increase in the ophthalmic artery, may simply be due to elevated IOP [42].

20.5.2 Heidelberg Retinal Flowmeter

The HRF provides blood-flow data in subcapillary resolution. The flow measurements are in arbitrary units and their exact correlation to real flow data remains unclear. The software within the device may cause distortion since it includes areas with no vessels. A pixel-by-pixel analysis has been developed to exclude areas of no perfusion and has been found to be highly reproducible [43].

20.5.3 Canon Laser Blood Flowmetry

Retinal volumetric blood flow is calculated in absolute units. Although several studies report reproducible measurements of retinal blood flow in normal subjects, the evaluations are complicated and require careful interpretation [11, 12].

20.5.4 Laser Doppler Flowmetry

The measurements in laser Doppler flowmetry are of a relative nature. Since there is variation in vascular density and vessel orientation within the tissue sampled, inter-individual comparisons are generally not recommended. It is difficult to interpret the data since measured Doppler shifts may be from both the retinal or choroidal vasculature [44].

20.5.5 Retinal Vessel Analyzer

This technique only provides retinal vessel diameter in relation to time and location. The measurements of retinal vessel diameters are restricted to larger vessels and should be performed in subjects with clear ocular media.

20.5.6 Scanning Laser Ophthalmoscopy Angiography

Measurements of volumetric blood flow by SLO angiography are currently not feasible. The analysis of these measurements is time consuming and requires trained graders [16].

20.5.7 Pulsatile Ocular Blood Flowmeter/Pascal Dynamic Contour Tonometer

Currently, POBF and Pascal DCT are available for clinical use to assess certain ocular hemodynamic parameters [45]. Since they measure global pulsatile choroidal hemodynamics, their measurements may not correlate with the blood supply to the optic nerve. Despite the correlation between OPA and visual field indices, POBF/Pascal DCT is not proven to provide guidance in the clinical management of glaucoma patients.

20.5.8 Fourier Domain Doppler Optical Coherence Tomography (FD-OCT)

FD-OCT retinal blood-flow scans transect all retinal branch arteries and veins that emerge from the ONH, providing the basis for total retinal blood-flow measurement as an absolute value (μL/min) [20, 21]. Currently there is limited data on the device in relation to glaucoma progression (Fig. 20.3).

20.5.9 Retinal Oximetry

Methods of direct measurement of tissue oxygenation are a step toward revealing metabolism

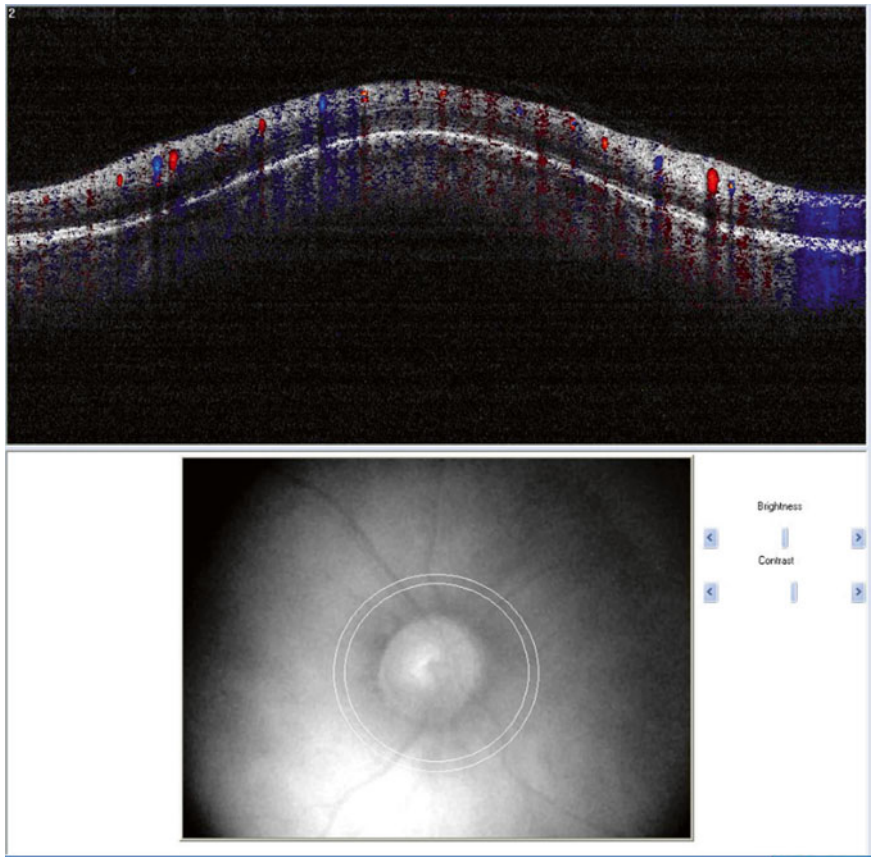

Fig. 20.3 FD-OCT image showing the unfolded cross-section from a circular scan. Arteries and veins could be distinguished by the direction of flow as determined by the signs (*blue* or *red* color) of the Doppler shift and the angle θ

and oxygen utilization in ophthalmic disease. However, significantly more research is needed to validate the true meaning of the parameters and their clinical impact in ocular diseases [40] (Fig. 20.4).

Summary for the Clinician

- Interpretation of ocular hemodynamics is complex, since no technique provides the measurement of blood flow itself.
- CDI: Peak systolic and end diastolic blood-flow velocities, which move in the same direction, represent a change in volumetric blood flow.
- HRF interpretation may be difficult, as the volume of tissue from which the data is collected may vary.
- Scanning laser ophthalmoscopy angiography permits velocity and dye circulation time calculation. Interpretation of these parameters in relation to the global retinal blood flow is not clear.
- FD-OCT has the promise of being more practical for clinical use as it combines OCT structure assessment with Doppler blood flow, however further research is necessary to validate their role in glaucoma management.

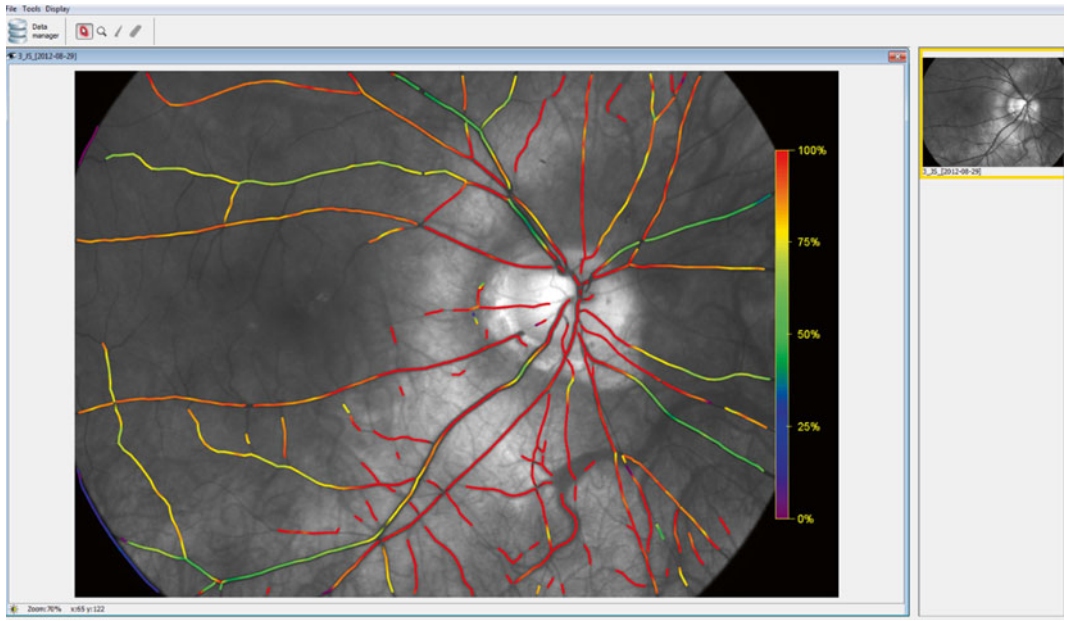

Fig. 20.4 Color overlay of oxygen saturation in the retinal vessels of a glaucoma subject showing decreased arterial venous difference in a fundus photograph taken from a spectral retinal oximeter

20.6 How Can the Data from Ocular Hemodynamic Studies Be Used in Clinical Practice?

It is clear that controlling IOP alone is not enough to prevent disease progression in some glaucoma patients. Several decades of evidence demonstrate that vascular risk factors contribute to disease prevalence, incidence, and progression. Several large population-based studies have shown that low ocular, and particularly low diastolic perfusion pressure, is an important consideration in glaucoma management [3–6]. Recently, the EMGT report found lower systolic perfusion pressure to be a predictor and an important risk factor for glaucoma progression [7]. Clinical practitioners can calculate ocular perfusion pressure by using systemic blood pressure and IOP measurements. Perfusion pressure is the difference between arterial and venous pressure. Since in the eye venous pressure is approximately equal to IOP, ocular perfusion pressure is calculated as 2/3 of the mean arterial blood pressure minus IOP. This can further be broken down into systolic and diastolic components by taking the systolic or diastolic blood pressure, respectively, minus the IOP [46]. In this capacity, it is strongly suggested that blood pressure measurements be taken during ophthalmic examinations and be evaluated in relation to IOP.

Nevertheless, there remains lack of a clear association between blood-flow deficiencies and structural optic nerve head changes or visual field progression in some glaucoma patients. Structural changes in the optic nerve have been reported to be related to abnormal ocular blood flow [47]. Reduced blood flow has been reported to correspond with areas of glaucomatous visual field loss [48]. Furthermore, normal-tension glaucoma patients with progressive visual field loss were found to have impaired blood-flow parameters compared with patients with stable visual fields [49]. Recent prospective evidence continues to confirm reductions in retrobulbar and retinal blood flow over time are associated with structural glaucomatous progression, as indicated by retinal and optic nerve changes [50]. Vascular deficits in glaucoma may also be prevalent in persons of African Descent [51] and glaucoma patients with diabetes [52].

Although the studies presented in this chapter highlight the established evidence for associations between ocular blood flow and structural and functional alterations, much larger, long-term, population-based studies and standardized technologies for clinical use are necessary to truly define the role of vascular deficits in glaucoma. Ocular blood-flow data is currently only a research tool and cannot guide patient treatment. Additional studies can determine whether interventions in blood pressure, perfusion pressure, or ocular blood flow may influence glaucoma progression.

Summary for the Clinician

- Low ocular perfusion pressure may be used to explain glaucoma progression even after reaching an optimal IOP.
- In progressive OAG, evaluation of a patient's blood pressure, perfusion pressure, and blood flow may be suggested.
- At present, ocular hemodynamic data cannot guide the way a patient with OAG is treated.
- Vascular deficits in glaucoma may also be prevalent in persons of African Descent and glaucoma patients with diabetes
- In future, sufficiently large long-term studies are needed to address the question of how changes in blood pressure, perfusion pressure, and ocular blood flow may alter glaucoma patients' outcome and whether ocular circulation interventions improve disease prognosis.

References

1. Leske MC, Wu SY, Hennis A, BESs Study Group, et al. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology. 2008;115:85–93.
2. Leske MC, Wu SY, Honkanen R, Group BES, et al. Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. Ophthalmology. 2007;114:1058–64.
3. Tielsh JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open-angle glaucoma. Arch Ophthalmol. 1995;113:216–21.
4. Leske MC, Wu SY, Nemesure B, et al. Incident open-angle glaucoma and blood pressure. Arch Ophthalmol. 2002;120:954–9.
5. Bonomi L, Marchini G, Marraffa M, et al. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. Ophthalmology. 2000;107:1287–93.
6. Quigley HA, West SK, Rodriguez J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol. 2001;119:1819–26.
7. Leske MC, Heijl A, Hyman L, Group EMGT, et al. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007;114(11):1965–72.
8. Harris A, Rechtman E, Siesky B, et al. The role of optic nerve blood flow in the pathogenesis of glaucoma. Ophthalmol Clin North Am. 2005;18(3):345–53.
9. Orge F, Harris A, Kagemann L, et al. The first technique for non-invasive measurements of volumetric ophthalmic artery blood flow in humans. Br J Ophthalmol. 2002;86(11):1216–9.
10. Jonescu-Cuypers CP, Harris A, Wilson R, et al. Reproducibility of the Heidelberg retinal flowmeter in determining low perfusion areas in peripapillary retina. Br J Ophthalmol. 2004;88(10):1266–9.
11. Feke GT. Laser Doppler instrumentation for the measurement of retinal blood flow: theory and practice. Bull Soc Belge Ophtalmol. 2006;302:171–84.
12. Yoshida A, Feke GT, Mori F, et al. Reproducibility and clinical application of a newly developed stabilized retinal laser Doppler instrument. Am J Ophthalmol. 2003;135:356–61.
13. Riva CE, Cranstoun SD, Grunwald JE, et al. Choroidal blood flow in the foveal region of the human ocular fundus. Invest Ophthalmol Vis Sci. 1994;35:4273–81.
14. Riva CE, Harino S, Petrig BL, et al. Laser Doppler flowmetry in the optic nerve. Exp Eye Res. 1992;55:499–506.
15. Blum M, Bachmann K, Wintzer D, et al. Noninvasive measurement of the Bayliss effect in retinal autoregulation. Graefes Arch Clin Exp Ophthalmol. 1999;237:296–300.
16. Rechtman E, Harris A, Kumar R, et al. An update on retinal circulation assessment technologies. Curr Eye Res. 2003;27(6):329–43.
17. Flower RW. Extraction of choriocapillaris hemodynamic data from ICG fluorescence angiogram. Invest Ophthalmol Vis Sci. 1993;34:2720–9.
18. Weizer JS, Asrani S, Stinnett SS, et al. The clinical utility of dynamic contour tonometry and ocular pulse amplitude. J Glaucoma. 2007;16(8):700–3.
19. Kerr J, Nelson P, O'Brien C. Pulsatile ocular blood flow in primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol. 2003;136(6):1106–13.
20. Wang Y, Lu A, Gil-Flamer J, et al. Measurement of total blood flow in the normal human retina using

Doppler Fourier-domain optical coherence tomography. Br J Ophthalmol. 2009;93(5):634–7.
21. Makita S, Fabritius T, Yasuno Y. Quantitative retinal-blood flow measurement with three-dimensional vessel geometry determination using ultrahigh-resolution Doppler optical coherence angiography. Opt Lett. 2008;33(8):836–8.
22. Hardarson SH, Harris A, Karlsson RA, et al. Automatic retinal oximetry. Invest Ophthalmol Vis Sci. 2006;47(11):5011–6.
23. Rankin SJA, Walman BE, Buckley AR, et al. Color Doppler imaging and spectral analysis of the optic nerve vasculature in glaucoma. Am J Ophthalmol. 1995;119:685–93.
24. Galassi F, Sodi A, Ucci F, et al. Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study. Arch Ophthalmol. 2003;121:1711–5.
25. Michaelson G, Longhans MJ, Groh MJM. Perfusion of the juxta-papillary retina and neuroretinal rim in primary open angle glaucoma. J Glaucoma. 1996;5: 91–8.
26. Sato EA, Ohtake Y, Shinoda K, et al. Decreased blood flow at neuroretinal rim of optic nerve head corresponds with visual field deficit in eyes with normal tension glaucoma. Graefes Arch Clin Exp Ophthalmol. 2006;244:795–801.
27. Feke GT, Pasquale LR. Retinal blood flow response to posture change in glaucoma patients compared with healthy subjects. Ophthalmology. 2007;115(2):246–52.
28. Boehm AG, Pillunat LE, Koeller U, et al. Regional distribution of optic nerve head blood flow. Graefes Arch Clin Exp Ophthalmol. 1999;237:484–8.
29. Nagel E, Vilser W, Lanzl IM. Retinal vessel reaction to short-term IOP elevation in ocular hypertensive and glaucoma patients. Eur J Ophthalmol. 2001;11: 338–44.
30. Garhofer G, Zawinka C, Resch H, et al. Response of retinal vessel diameters to flicker stimulation in patients with early open angle glaucoma. J Glaucoma. 2004;13:340–4.
31. Harris A, Jonescu-Cuypers CP, Kagemann L, et al. Effect of dorzolamide timolol combination versus timolol 0.5% on ocular blood flow in patients with primary open-angle glaucoma. Am J Ophthalmol. 2001;132(4):490–5.
32. Harris A, Chung HS, Ciulla TA, et al. Progress in measurement of ocular blood flow and relevance to our understanding of glaucoma and age-related macular degeneration: review. Prog Retin Eye Res. 1999;18(5):669–87.
33. Arend O, Remky A, Plange N, et al. A capillary density and retinal diameter measurements and their impact on altered retinal circulation in glaucoma: a digital fluorescein angiographic study. Br J Ophthalmol. 2002;86(4):429–33.
34. Marengo J, Ucha RA, Martinez-Cartier M, et al. Glaucomatous optic nerve head changes with scanning laser ophthalmoscopy. Int Ophthalmol. 2001;23:413–23.
35. O'Brart DP, de Souza LM, Bartsch DU, et al. Indocyanine green angiography of the peripapillary region in glaucomatous eyes by confocal scanning laser ophthalmoscopy. Am J Ophthalmol. 1997;123:657–66.
36. James CB, Smith SE. Pulsatile ocular blood flow in patients with low tension glaucoma. Br J Ophthalmol. 1991;75:466–70.
37. von Schulthess SR, Kaufmann C, Bachmann LM, et al. Ocular pulse amplitude after trabeculectomy. Graefes Arch Clin Exp Ophthalmol. 2006;244:46–51.
38. Wang Y, Fawzi AA, Varma R, et al. Pilot study of optical coherence tomography measurement of retinal blood flow in retinal and optic nerve diseases. Invest Ophthalmol Vis Sci. 2011;52(2):840–5.
39. Olafsdottir OB, Vandewalle E, Abegão Pinto L, et al. Retinal oxygen metabolism in healthy subjects and glaucoma patients. Br J Ophthalmol. 2014;98(3): 329–33.
40. Tobe LA, Harris A, Schroeder A, et al. Retinal oxygen saturation and metabolism: how does it pertain to glaucoma? An update on the application of retinal oximetry in glaucoma. Eur J Ophthalmol. 2013;23(4):465–72.
41. Spencer JA, Giussani DA, Moore PJ, et al. In vitro validation of Doppler indices using blood and water. J Ultrasound Med. 1991;10(6):305–8.
42. Harris A, Serra LM, Rechtman E, et al. Vascular abnormalities in glaucoma: from epidemiology to the clinic. Amadora: Impresse 4; 2005.
43. Mavroudis L, Harris A, Topouzis F, et al. Reproducibility of pixel-by-pixel analysis of Heidelberg retinal flowmetry images: the Thessaloniki Eye Study. Acta Ophthalmol Scand. 2008;86(1): 81–6.
44. Polska E, Polak K, Luksch A, et al. Twelve hour reproducibility of choroidal blood flow parameters in healthy subjects. Br J Ophthalmol. 2004;88:533–7.
45. Zion IB, Harris A, Siesky B, et al. Pulsatile ocular blood flow: relationship with flow velocities in vessels supplying the retina and choroid. Br J Ophthalmol. 2007;91(7):882–4.
46. Sehi M, Flanagan JG, Zeng L, et al. Relative change in diurnal mean ocular perfusion pressure: a risk factor for the diagnosis of primary open-angle glaucoma. Invest Ophthalmol. 2005;46:561–7.
47. Logan JF, Rankin SJ, Jackson AJ. Retinal blood flow measurements and neuroretinal rim damage in glaucoma. Br J Ophthalmol. 2004;88(8):1049–54.
48. Satilmis M, Orgül S, Doubler B, et al. Rate of progression of glaucoma correlates with retrobulbar circulation and intraocular pressure. Am J Ophthalmol. 2003;135(5):664–9.
49. Yamazaki Y, Drance SM. The relationship between progression of visual field defects and retrobulbar circulation in patients with glaucoma. Am J Ophthalmol. 1997;124(3):287–95.
50. Tobe LA, Harris A, Hussain RM, et al. The role of retrobulbar and retinal circulation on optic nerve head and retinal nerve fibre layer structure in patients with open-angle glaucoma over an 18-month period. Br J Ophthalmol. 2015;99:609–12.
51. Kanakamedala P, Harris A, Siesky B, et al. Optic nerve head morphology in glaucoma patients of African descent is strongly correlated to retinal blood flow. Br J Ophthalmol. 2014;98(11):1551–4.
52. Gerber AL, Harris A, Siesky B, et al. Vascular dysfunction in diabetes and glaucoma: a complex relationship reviewed. J Glaucoma. 2015;24(6):474–9.

Other Tests in Glaucoma: Multifocal Visual Evoked Potential

21

Donald C. Hood and Robert Ritch

Core Messages

- The multifocal visually evoked potential (mfVEP) provides an objective, topographical measure of local glaucomatous damage.
- The mfVEP can help in deciding upon treatment in patients with inconclusive visual field and disc examinations and when optical coherence tomography (OCT) scans are ambiguous or difficult to obtain.
- Prolonged latency of the mfVEP can signal a contribution from retinal disease, compressive tumors, or optic tract demyelinating disease.
- The mfVEP is not recommended as a replacement for standard automated perimetry (SAP) and/or OCT testing.
- The mfVEP is not recommended for routine screening of glaucoma suspects.
- The test is best performed at centers capable of recording and interpreting mfVEPs.

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21.1 What Is a Multifocal Visual Evoked Potential (mfVEP)?

21.1.1 The Visual Evoked Potential

Numerous electrophysiological tests have been proposed for detecting glaucomatous damage. Some involve electrical recordings from the eye, while others involve recordings from the cortex [1]. The focus of this chapter is on the latter, particularly the Visual Evoked Potential (VEP), an electrical potential recorded with one or more electrodes placed over the occipital region of the skull. A variety of visual displays have been used to record VEPs and standards are available that describe clinical recording and analysis of the "conventional" VEP [2]. While the VEP is useful in the diagnosis of a variety of conditions [3], to date there is no convincing evidence that any of the standard VEP procedures perform better than SAP for detecting glaucomatous damage. However, a relatively new technique, the multifocal VEP (mfVEP), can be clinically useful.

21.1.2 The Multifocal Visual Evoked Potential

The mfVEP is a potential recorded from the same occipital region with the same electrodes as the conventional VEP [4, 5]. However, while the standard VEP produces a response to a single

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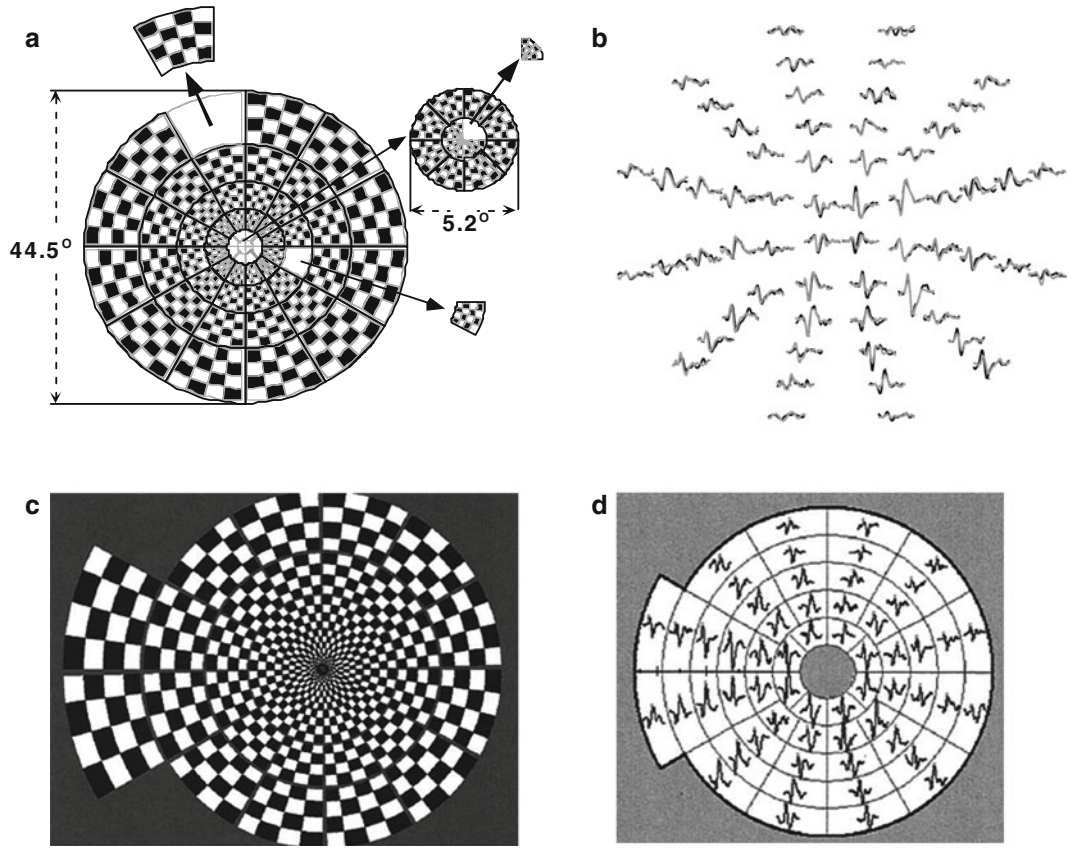

Fig. 21.1 (**a**) The display we employ for mfVEP recording [5, 6]. The insets illustrate the relative sizes of the individual sectors. (**b**) Responses obtained with display in (**a**). (**c**) The display employed in mfVEP recording by Graham et al. [7–9]. (**d**) Responses obtained with display in *panel B. Panels C* and *D* are modified from [7] and reproduced with permission

visual stimulus, the mfVEP allows the simultaneous measurement of many small VEP responses from a central field of vision. Figure 21.1a–c shows two displays to stimulate the eyes that have been used: the one we use (panel A) produced by VERIS (EDI, San Mateo, CA) [5, 6] and the one used by Graham et al. [7–9]. The display in Fig. 21.1a has 60 sectors, each a black and white checkerboard with 16 elements. As illustrated in the insets, the sectors increase in area with retinal eccentricity. The sectors of this pattern stimulate roughly the same area of the occipital cortex and produce mfVEP responses of roughly the same size, as shown in Fig. 21.1b. The display in Fig. 21.1c is similar in size and composition. Both displays cover about the same extent of the visual field, roughly a diameter of 50°, as does the 24-2 SAP test of the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA). The display in Fig. 21.1c, configured for stimulation of the right eye, has two sectors that extend into the region of the nasal step.

With the mfVEP technique, multiple VEP responses can be measured simultaneously. Although these waveforms are technically mathematical abstractions rather than little VEP responses [5, 10], we refer them here as "responses." Figure 21.1b, d show the local responses for the displays in Fig. 21.1a, c. Each of the small waveforms is a response elicited by the corresponding checkerboard sector. In Fig. 21.1b, the black and gray responses are from the right and left eyes, respectively. The responses from the two eyes of an individual with normal vision are essentially identical [5, 6, 8].

The mfVEP provides topographical information. Each response in Fig. 21.1b, d is due to stimulation of a local region of the retina covered by the corresponding sector. The topographical nature of the response makes it possible to relate changes in mfVEP responses to local changes seen with SAP. As given below, local glaucomatous damage produces local changes in amplitude [5, 6, 9]. For reviews on this topic see references [5, 9, 11–13]. For alternative paradigms and analyses see references [14–18].

Summary for the Clinician

- The VEP is a potential recorded with one or more electrodes placed on the skin over the occipital region.
- The mfVEP technique yields multiple small VEP responses and provides topographical information about the health of local regions of the visual field.

21.2 How Do I Interpret the Results of mfVEP Tests?

21.2.1 Identifying Glaucomatous Damage

Figures 21.2 and 21.3 contain portions of the reports produced by the most common analysis programs to date, our analysis (Fig. 21.2) and the Graham and Klistorner analysis (Fig. 21.3). In both figures, panel A shows the 24-2 SAP field for one eye of a patient with glaucoma. The mfVEP report should have at least two parts.

First, there should be a display of the actual mfVEP responses as in panels (b) of Figs. 21.2 and 21.3. Each little wiggly line is a response, i.e., a plot of voltage vs. time. In Fig. 21.2b, the responses from both eyes are shown, coded as red (left eye) and blue (right eye). This patient had asymmetrical field loss between eyes and the 24-2 SAP field for the right eye (not shown) was normal. A close inspection of Fig. 21.3b reveals that the responses from the two eyes are essentially identical in some locations, while in other locations the responses from the left eye are clearly smaller than those from the right eye. With a little practice the clinician can learn to identify poor recordings (e.g., records with line noise or alpha) by examining the individual responses.

Second, there should be a topographical map indicating which of the individual responses are abnormal, i.e., outside normal confidence limits. In Fig. 21.2c, d this information is presented in a form similar to the total deviation plot (Fig. 21.2a) of the 24-2 SAP field. In particular, the red colored squares indicate sectors with responses that are significantly small at the 5 % (pale color) or 1 % (saturated color) significance level. In the monocular probability plot of Fig. 21.2c, the red squares indicate where the responses from the patient's left eye are significantly smaller than a normative group's response, while in Fig. 21.2d, the interocular probability plot, they indicate where the responses from the left eye are significantly smaller than those of the right eye. Because the responses from both eyes are essentially identical in an individual with normal vision (see Fig. 21.1b), the interocular comparison is particularly good for detecting unilateral damage.

Figure 21.3 shows similar plots produced by the Graham and Klistorner approach. Instead of colored squares, the sectors of the display are shaded in panels (c) and (d) to indicate significance at the 5 % (light gray), 2 % (dark gray), or 1 % (black) level.

21.2.2 The mfVEP Provides Topographical Information

The mfVEP has two main assets. First, it is objective, in the sense that the patient's state of attention has little or no influence on the responses [19]. Second, it provides topographical information. This information can be appreciated best if the results are presented in a form comparable to the results obtained from SAP. The results in Figs. 21.2 and 21.3 illustrate two approaches. In

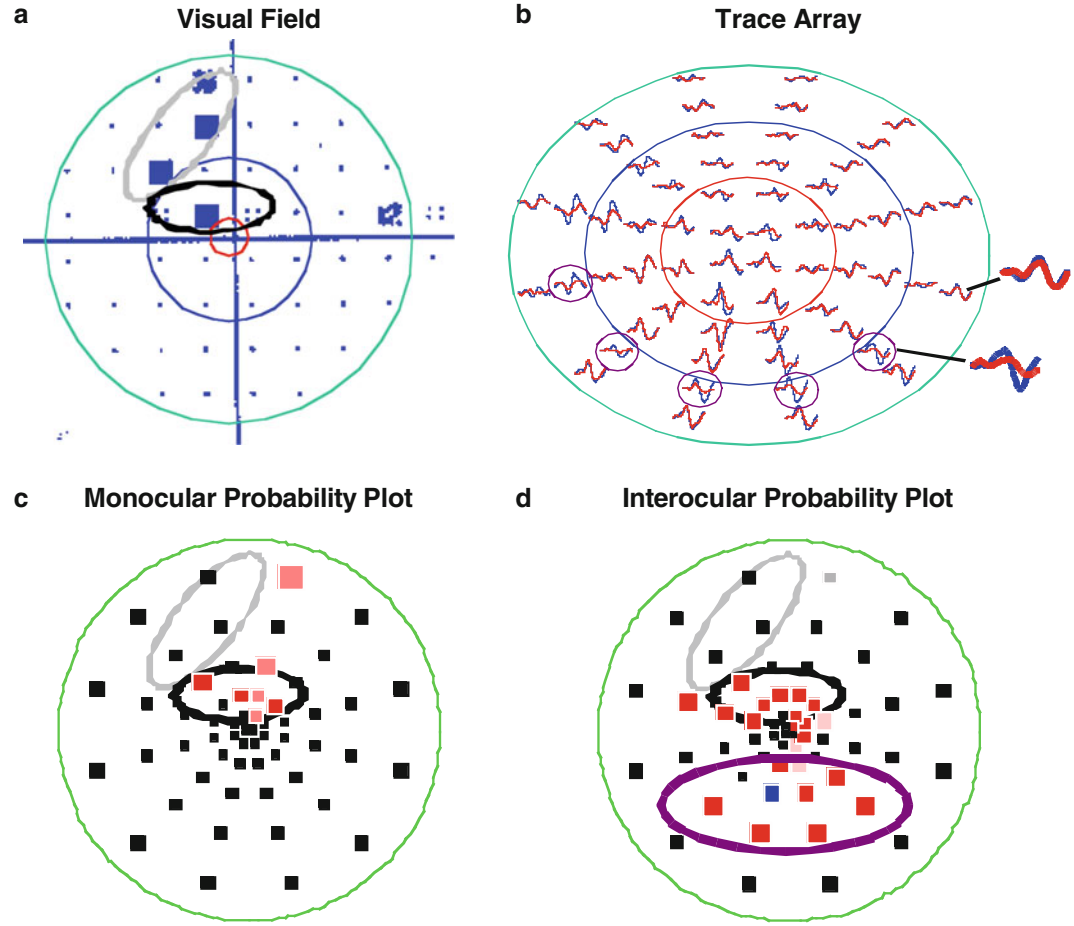

Fig. 21.2 (**a**) The 24-2 visual field of the right eye of a patient with asymmetric glaucomatous damage. (**b**) The mfVEP responses from both eyes of this patient. (**c**) A plot indicating the responses from the left eye (*red* records in *panel B*) that are abnormal at the 5 % (*pink*) or 1 % (*red*) significance level when compared to a normative database. (**d**) A similar plot showing that the responses from the left eye are abnormally smaller than those of the right eye, again as compared to a normative database. Significance levels are coded as in *panel C*, with *red* indicating that the response from the left eye is smaller than the response from the right eye and *blue* indicating the reverse. Modified from [12] and reproduced with permission

Fig. 21.2c, each square represents the center of one of the mfVEP displays plotted on linear coordinates as is done in SAP (e.g., Fig. 21.2a). If the monocular and interocular probability plots are plotted on a linear scale, they can be easily compared with any perimetric printout. For this patient, the 24-2 SAP test detected visual field damage (gray ellipse) that was missed on the mfVEP test, while the mfVEP test picked up an arcuate defect (purple ellipse) missed by the 24-2 SAP test. A different approach is taken in Fig. 21.3c. Here the sectors of the mfVEP display are coded to indicate abnormal responses.

21.2.3 mfVEP Latency as an Indicator of Other Diseases

Latency of the individual responses can also be useful. In general, glaucoma produces relatively small changes in local mfVEP latency, with some patients showing small increases in latency compared with healthy controls [20–23]. Large increases in latency are associated with demyelinating diseases such as multiple sclerosis [24–30] and with compressive tumors [31], while moderate increases suggest retinal disease [32].

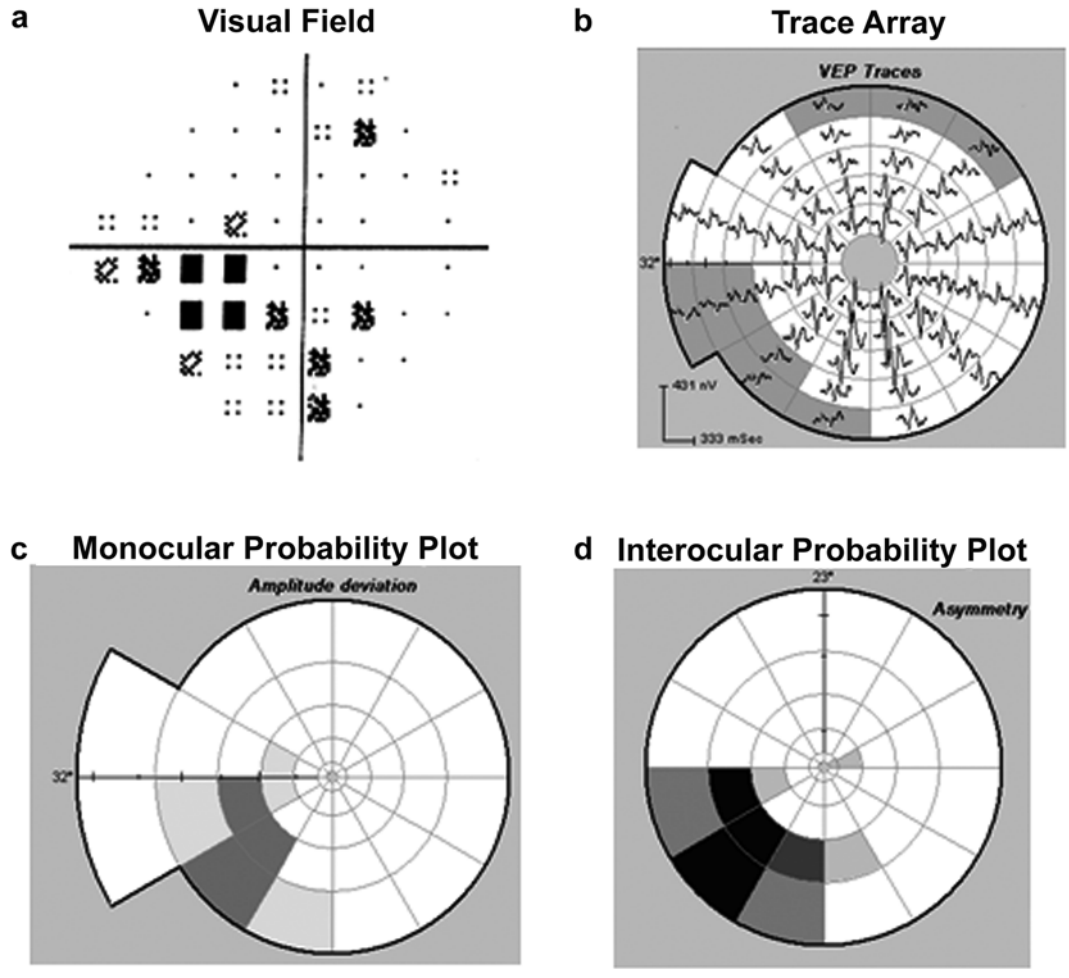

Fig. 21.3 (**a**) The 24-2 visual field of the right eye of a patient with glaucomatous damage. (**b**) The mfVEP responses from the same eyes. (**c**) A plot indicating the responses from this eye (records in *panel B*) that are abnormal at the 5 % (*light gray*), 2 % (*dark gray*) or 1 % (*black*) significance level when compared to a normative database. (**d**) A similar plot showing the responses from this eye that are abnormally smaller than those of the companion eye, again as compared to a normative database. Significance levels are coded as in *panel C*. Modified from [9] and reproduced with permission

Summary for the Clinician

- The mfVEP report should indicate those regions of the field in which the responses are abnormal.
- The presentation of abnormal regions should allow comparison to the patient's SAP field.
- Abnormal latencies should also be noted. Moderately prolonged latencies of mfVEP responses can signal the presence of retinal disease, while markedly prolonged latencies or increases in latency are associated with compressive tumors and multiple sclerosis.

21.3 Is the mfVEP a Useful Test in Glaucoma?

21.3.1 The mfVEP Is Not Ready for Routine Screening of Glaucoma Patients

The mfVEP is not recommended for routine screening in the typical clinical setting. First, the successful recording of mfVEPs requires specialized equipment. Presently, there is no commercially available product that can record and do an adequate job of analysis. Some devices can yield good recordings but they require specialized software, such as the programs we have written for mfVEP analysis [5, 6]. Second, trained personnel are needed for both the recording and its interpretation. Currently, mfVEP testing is best performed in centers with the necessary equipment, expertise, and experience. Finally, advances in OCT have diminished the need for an additional test. If OCT scans are carefully scrutinized and the results topographically compared to results from SAP [33–35], it can greatly reduced the number of eyes needing additional testing.

21.3.2 The mfVEP Can Provide Clinically Useful Information

The empirical and theoretical evidence suggest that the sensitivity and specificity of the mfVEP test are approximately the same as that of the 24-2 SAP test (e.g., [5, 36–38] and [39] for contrary data). However, in some patients the mfVEP can detect damage before it is detected by 24-2 SAP [5, 7, 9, 13, 37, 40], although in other patients the reverse is true. For example, the mfVEP can outperform the 24-2 SAP in cases of early damage where one eye is healthy and the responses are robust [5, 40]. Figure 21.2 illustrates this point; it shows the results obtained from a patient with an arcuate defect that was detected first with the mfVEP.

Until a few years ago, we routinely obtained mfVEPs from: (1) patients with conflicting SAP examinations. For example, in patients with a normal 24-2 SAP visual field, and an abnormal FDT and/or SWAP examination; (2) patients unable to produce reliable and consistent SAP visual fields as indicated by excessive fixation, false positive, and/or false negative errors; and (3) patients with visual fields inconsistent with other clinical findings, in particular fundus examination [5, 41].

Now, we routinely perform OCT scans and topographically compare the results to SAP results [34, 35, 42, 43]. We only consider a mfVEP test when the SAP and OCT results do not agree and the OCT scan is ambiguous (i.e., is not clearly normal or abnormal) and/or when the SAP results are unreliable and the OCT results are ambiguous.

Summary for the Clinician

- The mfVEP can detect glaucomatous damage before it is detected with SAP. For other patients, SAP is more sensitive.
- The mfVEP is not a substitute for SAP or for OCT scans.
- For patients in whom diagnosis by SAP, OCT and disc examination is uncertain, a mfVEP test may be beneficial. However, if OCT and SAP are analyzed correctly, this is a relatively small number of patients.
- The mfVEP is helpful in patients with unreliable SAP fields or whose fields are inconsistent with disc appearance and the OCT results ambiguous or difficult to obtain.
- Because of the difficulties involved in recording and analyzing mfVEPs, we recommend that the test be performed in centers with the necessary equipment, expertise, and experience.

References

1. Hood DC. Objective measurement of visual function in glaucoma. Cur Opin Ophthalmol. 2003;14:78–82.
2. Holder GE, Brigell MG, Hawlina M, Meigen T, Vaegan, Bach M, International Society for Clinical

Electrophysiology of Vision. ISCEV standard for clinical pattern electroretinography—2007 update. Doc Ophthalmol. 2007;114:111–6.
3. Brigell MG. The visual evoked potential. In: Fishman GA, Birch DG, Holder GE, Brigell MG, editors. Electrophysiologic testing in disorders of the retina, optic nerve, and visual pathway, Ophthalmology Monographs. 2nd ed. San Francisco: The Foundation of the American Academy of Ophthalmology; 2001. p. 237–78.
4. Baseler HA, Sutter EE, Klein SA, Carney T. The topography of visual evoked response properties across the visual field. Electroencephalogr Clin Neurophysiol. 1994;90:65–81.
5. Hood DC, Greenstein VC. The multifocal VEP and ganglion cell damage: applications and limitations for the study of glaucoma. Prog Retin Eye Res. 2003;22:201–51.
6. Hood DC, Zhang X, Greenstein VC, et al. An interocular comparison of the multifocal VEP: a possible technique for detecting local damage to the optic nerve. Invest Ophthalmol Vis Sci. 2000;41:1580–7.
7. Goldberg I, Graham SL, Klistorner AI. Multifocal objective perimetry in the detection of glaucomatous field loss. Am J Ophthalmol. 2002;133:29–39.
8. Graham SL, Klistorner AI, Grigg JR, Billson FA. Objective VEP perimetry in glaucoma: asymmetry analysis to identify early deficits. J Glaucoma. 2000;9:10–9.
9. Graham SL, Klistorner AI, Goldberg I. Clinical application of objective perimetry using multifocal visual evoked potentials in glaucoma practice. Arch Ophthalmol. 2005;123:729–39.
10. Fortune B, Hood DC. Conventional pattern-reversal VEPs are not equivalent to summed multifocal VEPs. Invest Ophthalmol Vis Sci. 2003;44:1364–7.
11. Hood DC. Electrophysiologic imaging of retinal and optic nerve damage: the multifocal technique. Ophthalmol Clin North Am. 2004;17:69–88.
12. Hood D, Odel JG, Winn BJ. The multifocal visual evoked potential (VEP): applications and limitations in neuro-ophthalmology. J Neuro Ophthalmol. 2003;23:279–89.
13. Klistorner A, Graham SL. Objective perimetry in glaucoma. Ophthalmology. 2000;107:2283–99.
14. James AC, Ruseckaite R, Maddess T. Effect of temporal sparseness and dichoptic presentation on multifocal visual evoked potentials. Vis Neurosci. 2005; 22:45–54.
15. Zhang X, Wang M, Hood D. Simultaneous recording of multifocal VEP responses to short-wavelength and achromatic stimuli. Doc Ophthalmol. 2010;121: 93–102.
16. Arvind H, Graham S, Leaney J, et al. Identifying preperimetric functional loss in glaucoma: a blue-on-yellow multifocal visual evoked potentials study. Ophthalmology. 2009;116:1134–41.
17. Arvind H, Klistorner A, Grigg J, Graham S. Low-luminance contrast stimulation is optimal for early detection of glaucoma using multifocal visual evoked potentials. Invest Ophthalmol Vis Sci. 2011;52: 3744–50.
18. Mousa MF, Cubbidge RP, Al-Mansouri F, Bener A. Evaluation of hemifields sector analysis protocol in multifocal visual evoked potential objective perimetry for the diagnosis and early detection of glaucomatous field defects. Korean J Ophthalmol. 2014;28: 49–65.
19. Seiple W, Holopigian K, Clemens C, et al. The multifocal visual evoked potential: an objective measure of visual field? Vision Res. 2005;45:1155–63.
20. Grippo TM, Hood DC, Kanadani FN, et al. A comparison between multifocal and conventional VEP latency changes secondary to glaucomatous damage. Invest Ophthalmol Vis Sci. 2006;47:5331–6.
21. Hood DC, Chen JY, Yang EB, et al. The role of the multifocal visual evoked potential (mfVEP) latency in understanding optic nerve and retinal diseases. Trans Am Ophthalmol Soc. 2006;104:71–7.
22. Klistorner A, Graham SL, Martins A, et al. Multifocal blue-on-yellow visual evoked potentials in early glaucoma. Ophthalmology. 2007;114:1613–21.
23. Rodarte C, Hood DC, Yang EB, et al. The effects of glaucoma on the latency of the multifocal visual evoked potential. Br J Ophthalmol. 2006;90:1132–6.
24. Hood DC, Odel JG, Zhang X. Tracking the recovery of local optic nerve function after optic neuritis: a multifocal VEP study. Invest Ophthalmol Vis Sci. 2000;41:4032–8.
25. Narayanan D, Cheng H, Tang RA, Frishman LJ. Reproducibility of multifocal vsual evoked potential and traditional visual evoked potential in normal and multiple sclerosis eyes. Doc Ophthalmol. 2015; 130:31–41.
26. Pérez-Rico C, Ayuso-Peralta L, Rubio-Pérez L, et al. Evaluation of visual structural and functional factors that predict the development of multiple sclerosis in clinically isolated syndrome patients. Invest Ophthalmol Vis Sci. 2014;55:6127–31.
27. Laron M, Cheng H, Zhang B, et al. Assessing visual pathway function in multiple sclerosis patients with multifocal visual evoked potentials. Mult Scler. 2009; 15:1431–41.
28. Laron M, Cheng H, Zhang B, et al. Comparison of multifocal visual evoked potential, standard automated perimetry and optical coherence tomography in assessing visual pathway multiple sclerosis patients. Mult Scler. 2010;16:412–26.
29. Fraser CL, Klistorner A, Graham SL, et al. Multifocal visual evoked potential analysis of inflammatory or demyelinating optic neuritis. Ophthalmology. 2006; 113:323.
30. Grover LK, Hood DC, Ghadiali Q, et al. A comparison of multifocal and conventional visual evoked potential techniques in patients with optic neuritis/multiple sclerosis. Doc Ophthalmol. 2008;117:121–8.
31. Semela L, Yang EB, Hedges TR, et al. Multifocal visual evoked potential in unilateral compressive optic neuropathy. Br J Ophthalmol. 2007;91: 445–8.

32. Chen JY, Hood DC, Odel JG, Behrens MM. The effects of retinal abnormalities on the multifocal visual evoked potential. Invest Ophthalmol Vis Sci. 2006;47:4378–85.
33. Hood DC, Raza AS. Method for comparing visual field defects to local RNFL and RGC damage seen on frequency domain OCT in patients with glaucoma. Biomed Opt Express. 2011;2:1097–105.
34. Hood DC, Raza AS. On improving the use of OCT imaging for detecting glaucomatous damage. Br J Ophthalmol. 2014;98 Suppl 2:ii1–9.
35. Hood DC, Raza AS, De Moraes CG, et al. Evaluation of a one-page report to aid in detecting glaucomatous damage. Transl Vis Sci Technol. 2014;3(6):8.
36. Fortune B, Demirel S, Zhang X, et al. Comparing multifocal VEP and standard automated perimetry in high-risk ocular hypertension and early glaucoma. Invest Ophthalmol Vis Sci. 2007;48:1173–80.
37. Thienprasiddhi P, Greenstein VC, Chu DH, et al. Detecting early functional damage in glaucoma suspect and ocular hypertensive patients with the multifocal VEP technique. J Glaucoma. 2006;15:321–7.
38. Nakamura M, Ishikawa K, Nagai T, Negi A. Receiver-operating characteristic analysis of multifocal VEPs to diagnose and quantify glaucomatous functional damage. Doc Ophthalmol. 2011;123:93–108.
39. Kanadani FN, Mello PA, Dorairaj SK, Kanadani TC. Frequency-doubling technology perimetry and multifocal visual evoked potential in glaucoma, suspected glaucoma, and control patients. Clin Ophthalmol. 2014;8:1323–30.
40. Hood DC, Thienprasiddhi P, Greenstein VC, et al. Detecting early to mild glaucomatous damage; a comparison of the multifocal VEP and automated perimetry. Invest Ophthalmol Vis Sci. 2004;45:492–8.
41. De Moraes CG, Liebmann JM, Ritch R, Hood DC. Clinical use of multifocal visual-evoked potentials in a glaucoma practice: a prospective study. Doc Ophthalmol. 2012;125(1):1–9.
42. Hood DC, Raza AS, de Moraes CGV, et al. Glaucomatous damage of the macula. Prog Retin Eye Res. 2013;32:1–21.
43. Hood DC, Slobodnick A, Raza AS, et al. Early glaucoma involves both deep local, and shallow widespread, retinal nerve fiber damage of the macular region. Invest Ophthalmol Vis Sci. 2014;55:632–49.

Risk Factors

22

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Core Messages

- Data from a number of prospective and cross-sectional studies show us that the risk of blindness from glaucoma is relatively low if diagnosed early and treated, but yet not zero.
- Risk factors for primary open-angle glaucoma (POAG) include demographic, genetic, ocular, and systemic factors.
- Highly myopic eyes may have a different risk of glaucoma and glaucomatous progression.

22.1 When I Diagnose a Patient with Glaucoma for the First Time, What Can I Tell Him/Her About the Risk of Going Blind from Glaucoma?

POAG is a less aggressive disease compared to angle-closure glaucoma and exfoliative glaucoma. There is evidence regarding the natural course of untreated glaucoma thanks to the St. Lucia study and the Early Manifest Glaucoma Trial (EMGT). In the St. Lucia Study, 29 % of eyes that were reexamined after 10 years had developed end-stage glaucoma, while 16 % of patients were blind in at least one eye [1]. Most patients were untreated during the 10-year interval between exams. In the EMGT, 76 % of untreated early glaucoma patients progressed (according to sensitive study criteria for progression on visual fields) after a median follow-up of 8 years, although specific data regarding rates of blindness are not available [2]. The risk of glaucoma deterioration was higher in eyes with pseudoexfoliative glaucoma.

The risk of going blind from treated glaucoma in the developed world is fairly small, especially if glaucoma is detected early enough and adequately treated. Hattenhauer et al. reported long-term outcomes of patients followed between 1965 and 1980 in Olmsted County, Minnesota [3], a period of time when available medical treatment was limited to miotics and nonselective adrenergic agonists. The risk of unilateral blindness from glaucoma in that study was calculated to be about 27 % at 20 years, while the risk of bilateral blindness was 9 %, i.e., roughly one-fourth of patients developed unilateral blindness and one in ten developed bilateral blindness secondary to glaucoma. In a more report from the same geographic area [4], the investigators found that rates of blindness decreased in the time period between 1981

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and 2000 as compared to the preceding two decades (1965–1980) [4]. For example, the probability of blindness in at least one eye decreased from 26 % in patients diagnosed in 1965–1980 to 14 % for those diagnosed in 1981–2000 ($p=0.01$). Other recent estimates confirm that under the care of glaucoma specialists with current management strategies, this risk may be as low as 15 % for unilateral blindness and 6 % for bilateral blindness at 15 years [5, 6]. In most studies, blindness has been defined as visual field constriction to within 10° of fixation or visual acuity of 20/200 or worse [3, 4, 6, 7]. Extrapolations made from cross-sectional data also support the notion that the risk of going blind from glaucoma is fairly low [7]. This risk has been estimated to be about 4 % for US whites and 8 % for US African-Americans with glaucoma [8, 9]. These risk estimates may be twice as high in developing countries.

The average duration of recognized glaucoma before death in whites and African-Americans has been estimated to be 13 and 16 years, respectively [10]. In a recent study of deceased glaucoma patients, the median duration of glaucoma before death was 12 years (range <1–29 years) [11]. Similar results have been reported from Finland [12]. With increasing longevity, however, glaucoma patients will likely be living longer with glaucoma. The major risk factors for going blind from glaucoma are age, poor compliance with treatment, and severity of glaucoma at diagnosis [4, 6, 13, 14]. The more advanced the glaucoma is at the time of diagnosis, the more likely it is to lead to blindness during a patient's lifetime [8, 13].

Summary for the Clinician

- The risk of progression to *bilateral* blindness in *treated* POAG is fairly low. Estimates from 2001 to 2003 place the risk at about 6 % at 15 years.
- The risk of progression to *unilateral* blindness in treated POAG from these same studies is about 15 % at 15 years.
- In most patients glaucoma is diagnosed within 15 years of death, so the risk of going blind from glaucoma past 15 years may be less relevant to the average patient. However, as longevity increases this may change.
- The risk factors for progression to blindness include older age, poor compliance with treatment, and more advanced glaucoma at diagnosis.

22.2 What Are the Main Risk Factors for Primary Open-Angle Glaucoma?

A risk factor is something that increases a person's chances of developing a disease. Different risk factors are sometimes detected by different study designs (cross-sectional vs. incidence studies). Knowledge of POAG risk factors is important and practical in two settings: (a) for screening purposes: money and efforts are best relegated to screening people in higher risk categories and (b) for detection purposes: each patient encounter in a general ophthalmology or glaucoma specialty clinic is a chance for risk stratification. For example, risk stratification can be used to dismiss the short- and intermediate-term risks of glaucoma in a 15-year-old teenager seeking an eye exam for astigmatism correction. On the other hand, risk stratification would cause one to spend more time examining the nerve and performing visual field testing in a 70-year-old diabetic woman with a family history of glaucoma, borderline pressures, and possible early signs of pseudoexfoliation syndrome.

Something to keep in mind when thinking about risk factors is that they can be divided into various categories. There are modifiable and nonmodifiable risk factors. For example, intraocular pressure (IOP) is the only known modifiable risk factor for POAG. Also, some risk factors, such as disc hemorrhages or cup-to-disc asymmetry, can be conceptually thought of as

early signs of the disease, which can confuse matters. Some risk factors are so common that they do not automatically lead to a diagnosis of "glaucoma suspect" per se. These are risk factors detected in large population-based studies (age, gender, race, myopia, central corneal thickness (CCT), and possibly systemic risk factors, such as diabetes and systemic hypertension) and are so frequent in people without glaucoma that they do not have strong discriminating power. Others, such as a positive family history, portend probable genetic predisposition.

Findings from the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS) have provided a practical framework for risk estimation in eyes with ocular hypertension [15]. However, in a recent study, despite adequate training in the results of OHTS, general ophthalmologists varied in their ability for intuitive estimation of the risk of progression in ocular hypertensive eyes [16]. In eyes without elevated IOP, our knowledge of the prognostic significance of the various risk factors identified by OHTS and EGPS remains inadequate so that a quantitative estimation of the probability of development of glaucoma is not yet possible. In these cases, clinicians commonly use some kind of intuitive extrapolation to sum up the risk factor profile for a particular patient. There is data to support the notion that risk estimation for progression can be valuable in eyes with established glaucoma. There are no available clinical tools as yet for this purpose. This risk estimation was based on a set of predictors consisting of age, CCT, history of disc hemorrhage, peak IOP and mean IOP, presence of beta peripapillary atrophy or exfoliation syndrome, and a history of glaucoma surgery [17]. In a recent meta-analysis, older age, occurrence of disc hemorrhages (for NTG eyes), baseline severity of visual field loss, baseline IOP level, presence of exfoliation syndrome, thinner CCT, presence of peripapillary atrophy (in NTG eyes), and proven prior visual field progression were found to be strongly associated with glaucoma progression [18].

22.2.1 Intraocular Pressure: The Sole Treatable Risk Factor for Glaucoma

Almost all population-based studies of prevalence and incidence have identified IOP as a risk factor for the presence or development of glaucoma [19]. Long-term follow-up of patients with ocular hypertension (OHT) in clinical trials, such as OHTS and EGPS, has shown IOP to be a major risk factor for progression to glaucoma [20, 21]. Other long-term studies of glaucomatous populations have established the definitive role of IOP reduction in decreasing the risk of glaucoma progression [22, 23].

In the Barbados glaucoma incidence study, a consistent increase in relative risk (RR) for incident glaucoma was observed with increasing baseline IOP [24]. Compared to eyes with a baseline IOP < 12 mmHg, the unadjusted RR increased to 1.4 for those with baseline IOPs between 12 and 17 mmHg, to 7.4 for those with IOPs between 21 and 23 mmHg, and to 18.0 for participants with baseline IOPs of 25 mmHg or more. Also, when IOP was evaluated as a continuous variable, the risk of open-angle glaucoma (OAG) increased by 12 % with each 1 mmHg increase in IOP (RR = 1.12; 95 % CI, 1.08–1.16; $p < 0.0001$) [24]. The 4-year incidence of OAG among persons with OHT in the Barbados Eye Study was about 5 % [25]. Interestingly, the 9-year incidence in the same cohort was 11 %, on average 1 % per year, which suggests a linear rate of progression to glaucoma in eyes with elevated IOP [26]. Preliminary analysis of the incidence data from the Rotterdam Eye Study found that the risk of incident OAG increased by 16 % per each millimeter of mercury increment in the highest IOP of either eye [27]. Ocular hypertension at baseline, defined as IOP > 21 mmHg or use of glaucoma drops, led to a threefold higher risk for incident OAG (odds ratio 3.3). Similarly, The Visual Impairment Study in Australia found that every millimeter of mercury increase in the baseline IOP increased the risk of progression to possible or probable glaucoma by about 10 % [28]. This is consistent with recently reported data from India

(OR = 2.0 per 10 mmHg) [29] and results from the Los Angeles Latino Eye Study (OR = 1.18 per mmHg) [30]. However, one must point out that the relationship of IOP to glaucoma incidence seems to be exponential, and therefore, studies may not be directly comparable.

Findings from the OHTS and EGPS have recently provided us with a framework that can be used to estimate the 5-year risk of developing glaucoma in a given patient. A prognostic study by the OHTS group showed that the main predictors for glaucoma development were advancing age, higher IOP, thinner CCT, a higher visual field pattern standard deviation, and a higher cup-to-disc ratio [20]. Specifically, the hazard ratio for conversion to glaucoma was shown to increase by 10 % for each mmHg increment in the baseline IOP. This finding has been confirmed by the EGPS. Higher baseline IOP increased the risk of progression to glaucoma by 7–18 % in that study [21]. Reduction of IOP has been found to be protective in preperimetric glaucoma as well [31].

Higher IOP fluctuation has been suggested as another risk factor for glaucoma progression, although this issue remains controversial [32–34]. The available evidence at this time does not support IOP fluctuation as a risk factor for progression of OHT to glaucoma [35, 36]. Other IOP parameters such as IOP peak have been found to be more important risk factors in treated glaucoma [37, 38].

22.2.2 Demographic Factors

- Age and gender
  Most studies have demonstrated increasing prevalence and incidence of glaucoma with advancing age. This is likely a function of longer disease duration in older individuals, although other factors may also be involved [19]. Higher age was also the main predictor of blindness from glaucoma in a recent long-term study [4]. Gender has not been found to be a clear-cut risk factor for OAG; however, in a recent meta-analysis, men were found to be at higher risk of having OAG (odds ratio = 1.37) [39].
- Ethnicity
  African-American and Hispanic ancestry have been shown to be associated with a higher incidence of glaucoma compared to white or Caucasian ethnicity [9, 40–42]. In a meta-analysis of 46 published studies, glaucoma prevalence was calculated to be at least two times higher in African-Americans (average of 4.2 %) compared to Caucasians (2.1 %) and Asians (1.4 %) [40]. A higher incidence of glaucoma has also has been found in other populations of African descent [43, 44]. People of African-American ancestry tend to be affected earlier (by almost a decade compared to whites) and are also more likely to go blind from glaucoma [41, 45]. This susceptibility is multifactorial and likely has both anatomic and socioeconomic causes [46]. African-Americans have thinner corneas and larger optic discs, and tended to have larger baseline cup-to-disc ratios in OHTS [20, 47]. They are also less likely to have access to appropriate care.
- Family history
  It has been shown that patients often inaccurately report a positive family history of glaucoma [48]. Despite this fact, the available evidence suggests that positive family history is a strong risk factor for glaucoma. In the Rotterdam Eye Study, all relatives of glaucoma cases were examined [49]. The RR for having glaucoma was 10 times higher in first-degree relatives of glaucoma cases. In the Barbados Family Study of Open-Angle Glaucoma, family members of a subgroup of 230 OAG cases were examined [50]. The authors found that almost 40 % of the probands had at least one affected family member. Twenty percent of siblings had OAG, and one-fourth of the family members had definite or suspected/probable OAG. A family history of glaucoma was reported to be four times higher in Tasmanian patients with POAG compared to a control population [51].

  A positive family history is likely a surrogate measure for a large number of genetic factors, such as predisposing genes, ana-

tomical factors leading to susceptibility (CCT, trabecular meshwork, and disc structure), and potentially environmental factors. An array of different mutations related to early-onset glaucoma and adult-onset glaucoma have been described. The three principal genes that have been found to be associated with adult OAG are myocilin (GLC1A), optineurin (GLC1E), and WDR36 (GLC1G) [52]. However, adult-onset POAG is a complex multifactorial disease and the above genes explain only a minority of POAG cases.

22.2.3 Pseudoexfoliation Syndrome and Pigment Dispersion Syndrome

Pseudoexfoliation syndrome is a strong risk factor for glaucoma development and is a very common cause of glaucoma in certain regions of the world, such as the Scandinavian countries, Greece, and the Middle East [53, 54]. The increased risk of developing glaucoma with pseudoexfoliation syndrome is observed even after adjusting for the effect of high IOP [28, 55, 56]. Pseudoexfoliation syndrome has been shown to increase risk of glaucoma by about ten times the baseline risk [28]. Similar results have been reported in the Tierp Sweden Eye (incidence) Survey (RR = 9.8) and the Blue Mountains Eye (prevalence) Study (odds ratio [OR] = 5.0) [55, 57]. In the Tierp Glaucoma Study, the effect of pseudoexfoliation was observed only at high IOPs (≥25 mmHg) [58]. Similarly, pigment dispersion syndrome is considered to be a risk factor for glaucoma, although no population-based studies with strict criteria have been carried out. In a recent retrospective study, the 5- and 15-year risk of glaucoma development in eyes with pigment dispersion syndrome followed in Olmsted County, Minnesota, was estimated at 10 % and 15 %, respectively [59].

22.2.4 Central Corneal Thickness

The role of CCT with regard to Goldman applanation tonometry (GAT) and the risk of glaucoma conversion or progression have recently been clarified. Briefly, the IOP measurements by GAT are most accurate for a CCT of about 520 μm. In eyes with a CCT that considerably deviates from this "average" number, the IOP would be underestimated (in thinner corneas) or overestimated (in thicker corneas) [60–62]. Various formulas have been devised to "correct" for the effect of CCT on GAT [62]. However, this effect may not be linear and CCT was shown to remain a risk factor even after correcting for its effect on IOP measurement in OHTS [61, 63]. Findings from OHTS and EGPS have confirmed that a fairly large number of patients with the so-called ocular hypertension have thick corneas (25 % > 600 μm in OHTS) and that a thinner CCT is a strong predictor of progression to glaucoma in ocular hypertensive patients [20, 21, 64, 65]. Clinically, it makes sense to consider CCT more as a risk factor and to think of CCT as being thin, average, or thick using OHTS criteria (<555 μm, 555–588 μm, and >588 μm, respectively) [63]. A thinner CCT has also been shown to be associated with a higher likelihood of glaucoma progression [2, 66, 67] although there are some data to the contrary [68, 69]. This effect may be IOP dependent, with eyes with higher IOPs and thinner CCTs being at highest risk [2, 30]. Recent reports have indicated that corneal hysteresis, an indicator of corneal viscoelastic properties, was a better predictor of glaucoma deterioration compared with CCT, confirming a prior retrospective study [70, 71]. More data are needed before the clinical utility of hysteresis can be fully established.

22.2.5 Systemic Factors

Although an increased systolic or diastolic BP has been found to be associated with a higher IOP [72], the relationship between systemic hypertension or diabetes mellitus and POAG remains inconclusive [19]. Lower blood pressure at night, especially a significant drop in BP has been found to be associated with worsening of glaucoma [73, 74].

More interesting is the relationship of ocular perfusion pressure and glaucoma. It appears that a

combination of lower blood pressure and higher IOP could potentially lead to a lower perfusion pressure and increase the risk of glaucoma [75, 76]. Recently, the Barbados Eye Study incidence data found that lower perfusion pressures were predictive of a higher incidence of OAG in a predominantly African-American population [77]. This is consistent with previous findings from other population-based surveys [78]. Interestingly, a longer-term report from EMGT found a lower perfusion pressure to be a risk factor for glaucoma progression as well [2]. This finding has been corroborated in other studies such as the Low-Pressure Glaucoma Treatment Study [79]. There is some evidence that higher fluctuation of ocular perfusion pressure may be an important risk factor for progression in normal tension glaucoma especially worsening in the central 10 degrees [80, 81]. Vascular dysregulation has also been suggested to be a major systemic risk factor for progression of glaucoma [78, 82].

Other systemic risk factors have been found to be associated with POAG [19, 83]. For some, such as migraine, the evidence is stronger than for others. These factors include history of migraine, cardiovascular diseases, sleep apnea syndrome, thyroid disorders, smoking, use of medications, specifically corticosteroids, and obesity as measured by waist to hip ratio. [30, 84].

Summary for the Clinician

- The main risk factors for glaucoma are higher IOP, advancing age, positive family history for glaucoma, African-American ancestry, and presence of pseudoexfoliation or pigment dispersion syndrome.
- A thinner CCT is a risk factor for development of glaucoma in eyes with ocular hypertension.

22.3 Is the Myopic Population at Higher Risk of Glaucoma? Do Myopic Patients with Glaucoma Progress Differently than Other Patients?

Although myopia has been associated with increasing prevalence of glaucoma in some studies [55, 85, 86], this has not been observed in most incidence studies or in OHTS and EGPS [28, 77]. In the Blue Mountain Study, the prevalence of glaucoma increased from 1.5 % in emmetropes to 4.4 % in moderate to high myopes [55]. In the Beijing Eye Study, myopia greater than −6.0 D increased the odds of having glaucoma fivefold compared to emmetropes [86]. Of note, the IOP levels were similar between the two groups, confirming findings from the Malmö Eye Survey that myopia is probably associated with glaucoma at lower IOP levels [87]. However, other investigators have found an association between myopia and higher IOP [88]. It is generally felt that eyes with high myopia can develop glaucoma and progress with pressures in the normal range. Interestingly, two recent longitudinal population-based studies demonstrated longer axial length to be a risk factor for incident glaucoma with a sizeable effect (OR = 1.5 per mm for both LALES and the Chennai Study) [29, 30].

It is often difficult to establish the presence of glaucoma or its progression in highly myopic eyes (myopia greater than −6 to −8 D) since these eyes commonly demonstrate degenerative myopic changes. Eyes with higher levels of myopia tend to have a higher prevalence of horizontally oval or tilted discs (see Chap. 13) and oblique insertion of the optic disc compared to emmetropic or hyperopic eyes [89]. Secondary acquired macrodiscs are also quite common [90]. The optic cup depth tends to be shallower in these eyes. Greve and Furuno reported that myopic eyes frequently demonstrated the following types of field defect: enlargement of the blind spot, superotemporal refractive scotomas, and irregular defects due to myopic degenerative

changes [91]. This adds to the difficulty of detecting glaucoma and its progression. There is scarce data regarding glaucoma progression in myopic eyes [92]. Some evidence suggests that myopia may be a risk factor for faster visual field progression in eyes with POAG [93, 94]; however, further study is needed to clarify this issue.

Summary for the Clinician

- Eyes with higher degrees of myopia seem to be at higher risk of glaucoma development.
- Eyes with high myopia may develop glaucoma at lower IOP levels.
- Evaluating the presence or progression of glaucomatous damage is difficult in eyes with high myopia due to changes in the optic disc configuration and nonspecific changes in the visual field.

References

1. Wilson MR. Progression of visual field loss in untreated glaucoma patients and suspects in St Lucia, West Indies. Trans Am Ophthalmol Soc. 2002;100:365–410.
2. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z. Predictors of long-term progression in the early manifest glaucoma trial. Ophthalmology. 2007;114(11):1965–72.
3. Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. Ophthalmology. 1998;105(11):2099–104.
4. Malihi M, Moura Filho ER, Hodge DO, Sit AJ. Long-term trends in glaucoma-related blindness in Olmsted County, Minnesota. Ophthalmology. 2014;121(1):134–41.
5. Kwon YH, Kim CS, Zimmerman MB, Alward WL, Hayreh SS. Rate of visual field loss and long-term visual outcome in primary open-angle glaucoma. Am J Ophthalmol. 2001;132(1):47–56.
6. Chen PP. Blindness in patients with treated open-angle glaucoma. Ophthalmology. 2003;110(4):726–33.
7. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90(3):262–7.
8. Quigley HA. Proportion of those with open-angle glaucoma who become blind. Ophthalmology. 1999;106(11):2039–41.
9. Quigley HA, West SK, Rodriguez J, Munoz B, Klein R, Snyder R. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol. 2001;119(12):1819–26.
10. Quigley HA, Vitale S. Models of open-angle glaucoma prevalence and incidence in the United States. Invest Ophthalmol Vis Sci. 1997;38(1):83–91.
11. Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. Am J Ophthalmol. 2013;156(4):724–30.
12. Forsman E, Kivelä T, Vesti E. Lifetime visual disability in open-angle glaucoma and ocular hypertension. J Glaucoma. 2007;16(3):313–9.
13. Grant WM, Burke JF. Why do some people go blind from glaucoma? Ophthalmology. 1982;89(9):991–8.
14. Oliver JE, Hattenhauer MG, Herman D, et al. Blindness and glaucoma: a comparison of patients progressing to blindness from glaucoma with patients maintaining vision. Am J Ophthalmol. 2002;133(6):764–72.
15. Gordon MO, Torri V, Miglior S, et al. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. Ophthalmology. 2007;114(1):10–9.
16. Mansberger SL, Cioffi GA. The probability of glaucoma from ocular hypertension determined by ophthalmologists in comparison to a risk calculator. J Glaucoma. 2006;15(5):426–31.
17. De Moraes CG, Sehi M, Greenfield DS, Chung YS, Ritch R, Liebmann JM. A validated risk calculator to assess risk and rate of visual field progression in treated glaucoma patients. Invest Ophthalmol Vis Sci. 2012;53(6):2702–7.
18. Ernest PJ, Schouten JS, Beckers HJ, Hendrikse F, Prins MH, Webers CA. An evidence-based review of prognostic factors for glaucomatous visual field progression. Ophthalmology. 2013;120(3):512–9.
19. Boland MV, Quigley HA. Risk factors and open-angle glaucoma: classification and application. J Glaucoma. 2007;16(4):406–18.
20. Gordon MO, Beiser JA, Brandt JD, et al. The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):714–20. Discussion 829–730.
21. Miglior S, Pfeiffer N, Torri V, Zeyen T, Cunha-Vaz J, Adamsons I. Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. Ophthalmology. 2007;114(1):3–9.
22. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol. 2000;130(4):429–440.

23. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268–79.
24. Nemesure B, Honkanen R, Hennis A, Wu SY, Leske MC. Incident open-angle glaucoma and intraocular pressure. Ophthalmology. 2007;114(10):1810–5.
25. Leske MC, Connell AM, Wu SY, et al. Incidence of open-angle glaucoma: the Barbados Eye Studies. The Barbados Eye Studies Group. Arch Ophthalmol. 2001;119(1):89–95.
26. Leske MC, Wu SY, Honkanen R, et al. Nine-year incidence of open-angle glaucoma in the Barbados Eye Studies. Ophthalmology. 2007;114(6):1058–64.
27. de Voogd S, Ikram MK, Wolfs RC, Jansonius NM, Hofman A, de Jong PT. Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. Ophthalmology. 2005;112(9):1487–93.
28. Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology. 2002;109(6): 1047–51.
29. Vijaya L, Rashima A, Panday M, et al. Predictors for incidence of primary open-angle glaucoma in a South Indian population: the Chennai eye disease incidence study. Ophthalmology. 2014;121(7):1370–6.
30. Jiang X, Varma R, Wu S, et al. Baseline risk factors that predict the development of open-angle glaucoma in a population: the Los Angeles Latino Eye Study. Ophthalmology. 2012;119(11):2245–53.
31. Kim KE, Jeoung JW, Kim DM, Ahn SJ, Park KH, Kim SH. Long-term follow-up in preperimetric open-angle glaucoma: progression rates and associated factors. Am J Ophthalmol. 2015;159(1):160–8.e161–2.
32. Bengtsson B, Leske MC, Hyman L, Heijl A. Fluctuation of intraocular pressure and glaucoma progression in the early manifest glaucoma trial. Ophthalmology. 2007;114(2):205–9.
33. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. Ophthalmology. 2008;115(7):1123–1129.e3.
34. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111(9):1627–35.
35. Bengtsson B, Heijl A. Diurnal IOP fluctuation: not an independent risk factor for glaucomatous visual field loss in high-risk ocular hypertension. Graefes Arch Clin Exp Ophthalmol. 2005;243(6):513–8.
36. Medeiros FA, Weinreb RN, Zangwill LM, et al. Long-term intraocular pressure fluctuations and risk of conversion from ocular hypertension to glaucoma. Ophthalmology. 2008;115(6):934–40.
37. De Moraes CG, Juthani VJ, Liebmann JM, et al. Risk factors for visual field progression in treated glaucoma. Arch Ophthalmol. 2011;129(5):562–8.
38. Gardiner SK, Johnson CA, Demirel S. Factors predicting the rate of functional progression in early and suspected glaucoma. Invest Ophthalmol Vis Sci. 2012;53(7):3598–604.
39. Rudnicka AR, Mt-Isa S, Owen CG, Cook DG, Ashby D. Variations in primary open-angle glaucoma prevalence by age, gender, and race: a Bayesian meta-analysis. Invest Ophthalmol Vis Sci. 2006;47(10): 4254–61.
40. Sommer A, Tielsch JM, Katz J, et al. Racial differences in the cause-specific prevalence of blindness in east Baltimore. N Engl J Med. 1991;325(20):1412–7.
41. Leske MC, Connell AM, Schachat AP, Hyman L. The Barbados Eye Study. Prevalence of open angle glaucoma. Arch Ophthalmol. 1994;112(6):821–9.
42. Varma R, Ying-Lai M, Francis BA, et al. Prevalence of open-angle glaucoma and ocular hypertension in Latinos: the Los Angeles Latino Eye Study. Ophthalmology. 2004;111(8):1439–48.
43. Buhrmann RR, Quigley HA, Barron Y, West SK, Oliva MS, Mmbaga BB. Prevalence of glaucoma in a rural East African population. Invest Ophthalmol Vis Sci. 2000;41(1):40–8.
44. Rotchford AP, Johnson GJ. Glaucoma in Zulus: a population-based cross-sectional survey in a rural district in South Africa. Arch Ophthalmol. 2002; 120(4):471–8.
45. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA. 1991;266(3):369–74.
46. Racette L, Wilson M, Zangwill L, Weinreb R, Sample P. Primary open-angle glaucoma in blacks: A review. Surv Ophthalmol. 2003;48(3):295–313.
47. Varma R, Tielsch JM, Quigley HA, et al. Race-, age-, gender-, and refractive error-related differences in the normal optic disc. Arch Ophthalmol. 1994;112(8): 1068–76.
48. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. Arch Ophthalmol. 1994;112(1):69–73.
49. Wolfs RC, Klaver CC, Ramrattan RS, van Duijn CM, Hofman A, de Jong PT. Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. Arch Ophthalmol. 1998;116(12):1640–5.
50. Leske MC, Nemesure B, He Q, Wu SY, Fielding Hejtmancik J, Hennis A. Patterns of open-angle glaucoma in the Barbados Family Study. Ophthalmology. 2001;108(6):1015–22.
51. Green CM, Kearns LS, Wu J, et al. How significant is a family history of glaucoma? Experience from the Glaucoma Inheritance Study in Tasmania. Clin Experiment Ophthalmol. 2007;35(9):793–9.
52. Wiggs JL. Genetic etiologies of glaucoma. Arch Ophthalmol. 2007;125(1):30–7.
53. Forsius H. Exfoliation syndrome in various ethnic populations. Acta Ophthalmol Suppl. 1988;184: 71–85.
54. Vesti E, Kivelä T. Exfoliation syndrome and exfoliation glaucoma. Prog Retin Eye Res. 2000;19(3): 345–68.

55. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology. 1999;106(10): 2010–5.
56. Grodum K, Heijl A, Bengtsson B. Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. Ophthalmology. 2005;112(3):386–90.
57. Ekström C. Prevalence of open-angle glaucoma in central Sweden. The Tierp Glaucoma Survey. Acta Ophthalmol Scand. 1996;74(2):107–12.
58. Ekström C. Risk factors for incident open-angle glaucoma: a population-based 20-year follow-up study. Acta Ophthalmol. 2012;90(4):316–21.
59. Siddiqui Y, Ten Hulzen RD, Cameron JD, Hodge DO, Johnson DH. What is the risk of developing pigmentary glaucoma from pigment dispersion syndrome? Am J Ophthalmol. 2003;135(6):794–9.
60. Ehlers N, Bramsen T, Sperling S. Applanation tonometry and central corneal thickness. Acta Ophthalmol (Copenh). 1975;53(1):34–43.
61. Feltgen N, Leifert D, Funk J. Correlation between central corneal thickness, applanation tonometry, and direct intracameral IOP readings. Br J Ophthalmol. 2001;85(1):85–7.
62. Kohlhaas M, Boehm AG, Spoerl E, Pürsten A, Grein HJ, Pillunat LE. Effect of central corneal thickness, corneal curvature, and axial length on applanation tonometry. Arch Ophthalmol. 2006;124(4):471–6.
63. Brandt JD. Central corneal thickness, tonometry, and glaucoma risk--a guide for the perplexed. Can J Ophthalmol. 2007;42(4):562–6.
64. Brandt JD, Beiser JA, Kass MA, Gordon MO. Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). Ophthalmology. 2001;108(10):1779–88.
65. Pfeiffer N, Torri V, Miglior S, Zeyen T, Adamsons I, Cunha-Vaz J. Central corneal thickness in the European Glaucoma Prevention Study. Ophthalmology. 2007; 114(3):454–9.
66. Medeiros F. Corneal thickness measurements and frequency doubling technology perimetry abnormalities in ocular hypertensive eyes. Ophthalmology. 2003;110(10):1903–8.
67. Medeiros FA, Sample PA, Weinreb RN. Corneal thickness measurements and visual function abnormalities in ocular hypertensive patients. Am J Ophthalmol. 2003;135(2):131–7.
68. Chauhan BC, Hutchison DM, LeBlanc RP, Artes PH, Nicolela MT. Central corneal thickness and progression of the visual field and optic disc in glaucoma. Br J Ophthalmol. 2005;89(8):1008–12.
69. Jonas JB. Central corneal thickness correlated with glaucoma damage and rate of progression. Invest Ophthalmol Vis Sci. 2005;46(4):1269–74.
70. Congdon NG, Broman AT, Bandeen-Roche K, Grover D, Quigley HA. Central corneal thickness and corneal hysteresis associated with glaucoma damage. Am J Ophthalmol. 2006;141(5):868–75.
71. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. Ophthalmology. 2013;120(8):1533–40.
72. Zhao D, Cho J, Kim MH, Guallar E. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. Am J Ophthalmol. 2014;158(3):615–627.e9.
73. Graham SL, Drance SM, Wijsman K, Douglas GR, Mikelberg FS. Ambulatory blood pressure monitoring in glaucoma. The nocturnal dip. Ophthalmology. 1995;102(1):61–9.
74. Charlson ME, de Moraes CG, Link A, et al. Nocturnal systemic hypotension increases the risk of glaucoma progression. Ophthalmology. 2014;121(10):2004–12.
75. Tielsch JM, Katz J, Sommer A, Quigley HA, Javitt JC. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. Arch Ophthalmol. 1995;113(2):216–21.
76. Bonomi L, Marchini G, Marraffa M, Bernardi P, Morbio R, Varotto A. Vascular risk factors for primary open angle glaucoma: the Egna-Neumarkt Study. Ophthalmology. 2000;107(7):1287–93.
77. Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. Ophthalmology. 2008;115(1): 85–93.
78. Tokunaga T, Kashiwagi K, Tsumura T, Taguchi K, Tsukahara S. Association between nocturnal blood pressure reduction and progression of visual field defect in patients with primary open-angle glaucoma or normal-tension glaucoma. Jpn J Ophthalmol. 2004;48(4):380–5.
79. De Moraes CG, Liebmann JM, Greenfield DS, et al. Risk factors for visual field progression in the low-pressure glaucoma treatment study. Am J Ophthalmol. 2012;154(4):702–11.
80. Choi J, Lee JR, Lee Y, et al. Relationship between 24-hour mean ocular perfusion pressure fluctuation and rate of paracentral visual field progression in normal-tension glaucoma. Invest Ophthalmol Vis Sci. 2013;54(9):6150–7.
81. Sung KR, Cho JW, Lee S, et al. Characteristics of visual field progression in medically treated normal-tension glaucoma patients with unstable ocular perfusion pressure. Invest Ophthalmol Vis Sci. 2011;52(2): 737–43.
82. Galassi F, Sodi A, Ucci F, Renieri G, Pieri B, Baccini M. Ocular hemodynamics and glaucoma prognosis: a color Doppler imaging study. Arch Ophthalmol. 2003;121(12):1711–5.
83. Leske MC. Open-angle glaucoma—an epidemiologic overview. Ophthalmic Epidemiol. 2007;14(4): 166–72.
84. Pache M, Flammer J. A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma. Surv Ophthalmol. 2006;51(3): 179–212.
85. Ramakrishnan R, Nirmalan PK, Krishnadas R, et al. Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. Ophthalmology. 2003;110(8):1484–90.
86. Xu L, Li Y, Wang S, Wang Y, Jonas JB. Characteristics of highly myopic eyes: the Beijing Eye Study. Ophthalmology. 2007;114(1):121–6.

87. Grødum K, Heijl A, Bengtsson B. Refractive error and glaucoma. Acta Ophthalmol Scand. 2001;79(6):560–6.
88. Wong TY, Klein BE, Klein R, Knudtson M, Lee KE. Refractive errors, intraocular pressure, and glaucoma in a white population. Ophthalmology. 2003;110(1):211–7.
89. Chihara E, Sawada A. Atypical nerve fiber layer defects in high myopes with high-tension glaucoma. Arch Ophthalmol. 1990;108(2):228–32.
90. Jonas JB, Gusek GC, Naumann GO. Optic disk morphometry in high myopia. Graefes Arch Clin Exp Ophthalmol. 1988;226(6):587–90.
91. Greve EL, Furuno F. Myopia and glaucoma. Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1980;213(1):33–41.
92. Nicolela MT, McCormick TA, Drance SM, Ferrier SN, LeBlanc RP, Chauhan BC. Visual field and optic disc progression in patients with different types of optic disc damage: a longitudinal prospective study. Ophthalmology. 2003;110(11):2178–84.
93. Perdicchi A, Iester M, Scuderi G, Amodeo S, Medori EM, Recupero SM. Visual field damage and progression in glaucomatous myopic eyes. Eur J Ophthalmol. 2007;17(4):534–7.
94. Schwartz B, Takamoto T, Martin J. Increased rate of visual field loss associated with larger initial visual field threshold values on follow-up of open-angle glaucoma. J Glaucoma. 2004;13(2):120–9.

Risk Factors: The Risk Calculator

23

Steven L. Mansberger

Core Messages

- The decision to treat an ocular hypertensive is a complex one.
- Current risk calculators determine the risk that an ocular hypertensive patient has for developing glaucoma over a 5-year period of time.
- Current risk calculators are only applicable to patients who resemble the population studied in the Ocular Hypertension Treatment Study (OHTS).

23.1 Is a Risk Calculator Useful?

Eye care providers can use calculators for determining the risk of developing glaucoma from ocular hypertension. Approximately 8 % of adults over the age of 40 in the United States have ocular hypertension [1]. While ocular hypertension is a common finding, eye care providers do not know which patients to treat or which patients to monitor without treatment [2].

Trying to decide whether to treat an ocular hypertension patient is complex without a risk calculator. The newest OHTS multivariate regression contains five variables that are predictive of developing glaucoma from ocular hypertension: age, central corneal thickness (CCT), intraocular pressure (IOP), pattern standard deviation (PSD), and vertical cup-to-disc ratio (C/D) [3]. Even if one simplifies the continuous variables of age, corneal thickness, IOP, and PSD into thirds and uses nine different combinations for C/D (0.0–0.8), 729 ($3\times3\times3\times3\times9$) different results exist for ocular hypertension patients. This creates a large number of combinations that are difficult for clinicians to decipher when deciding whether to treat a particular ocular hypertension patient.

One publication estimated an ophthalmologist's ability to predict the risk of glaucoma in ocular hypertensive patients [4]. Ophthalmologists had the benefit of an oral review and written handouts summarizing the OHTS results. Ophthalmologists tended to underestimate the risk when compared to the actual risk found by a risk calculator. They also had a large range of predictions, sometimes differing from the actual risk by 40 % (Fig. 23.1). In general, this study shows that eye care providers may frequently over- or under-treat their ocular hypertensive patients because of this difficulty in risk assessment. Predicting the development of glaucoma from ocular hypertension is a cornerstone in deciding whether or not to treat. Other useful risk calculators [5] may include the probability of progressive glaucoma [6] and successful glaucoma surgery.

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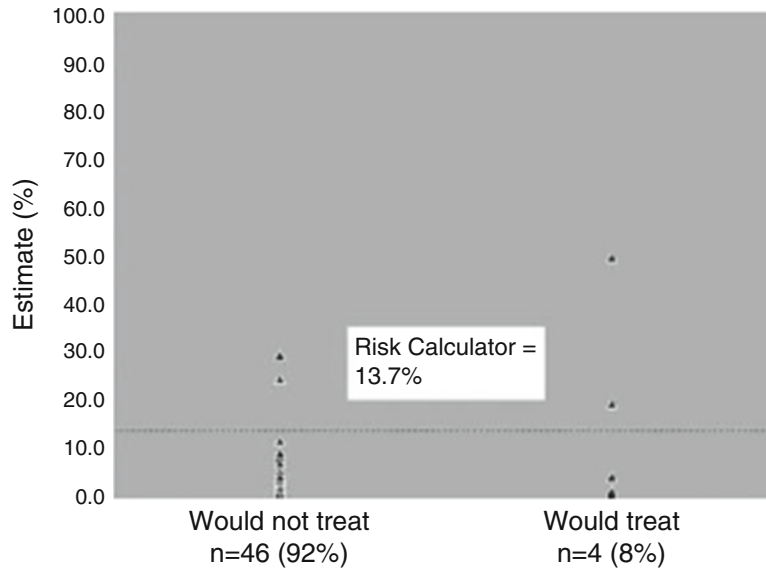

Fig. 23.1 Scatterplot of ophthalmologists' estimate of risk (%) and whether or not they would treat ocular hypertension. The *dashed line* within the figure represents the risk calculator estimate. Reproduced from [4]

Summary for the Clinician

- A current risk calculator available is based on results of an OHTS multivariate regression model.
- Five variables are predictive for an ocular hypertensive developing glaucoma: age, CCT, IOP, PSD, and vertical C/D ratio.
- The number of combinations between these five variables is enormous; the risk calculator helps to simplify the decision tree.
- Eye care providers frequently over- and under-treat ocular hypertensives compared to the risk calculator assessment.

23.2 How Should I Use a Risk Calculator?

One can obtain a risk calculator free of charge from the OHTS Web site (http://ohts.wustl.edu/risk) in web-based and Adobe Acrobat® versions. One simply enters the information into the calculator and then clicks the calculate button (Fig. 23.2).

Eye care providers can use a risk calculator in patients who are similar to the OHTS study population (OHTS inclusion criteria: age 40–80, IOP between 24 and 32 mmHg in the first eye and 21 and 32 mmHg in fellow eye, gonioscopically open angles, and no evidence of glaucomatous damage by nerve or visual field). For example, ophthalmologists should not assume that eyes with secondary causes of ocular hypertension (such as pseudoexfoliation or pigmentary dispersion syndrome) would have similar risk for conversion to glaucoma as the OHTS study population. A risk calculator can be imprecise if your patient has a combination of characteristics that were rare in OHTS, such as diabetes, a smaller C/D, a thicker cornea, and older age.

Clinicians should consider all of an individual patient's medical, ocular, and family history when deciding whether or not to treat the ocular hypertension. The current risk calculators do not include important information that should also guide treatment, such as medical health and life expectancy, a patient's willingness to commit to years of medical therapy, cost, and the effect of quality of life on treatment. Eye care providers should recognize that risk assessment is still evolving. Overall, eye care providers should consider the results of a risk calculator as supplemental information when managing an ocular hypertensive patient.

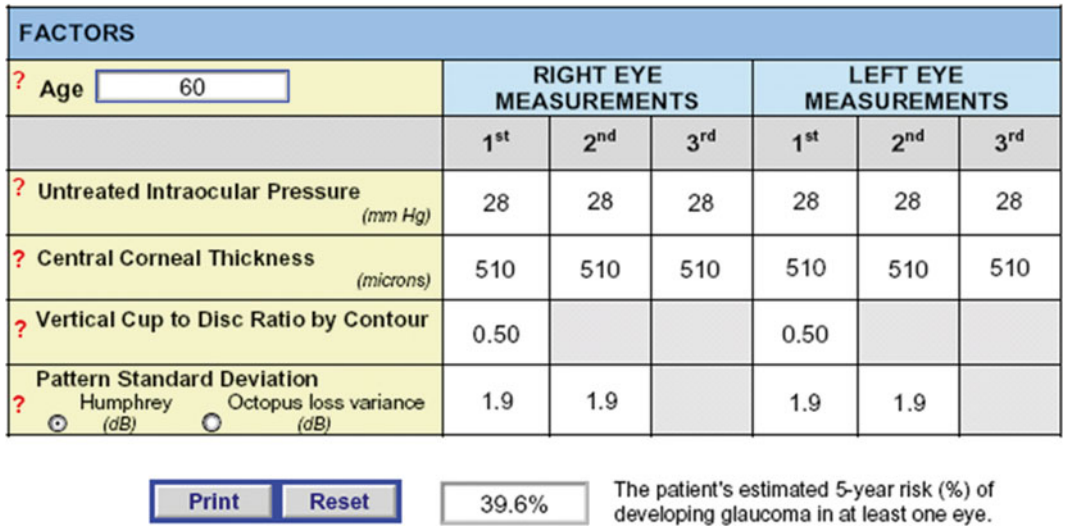

Fig. 23.2 Example of a current risk calculator. Available at the Ocular Hypertension Treatment Study Web site (http://ohts.wustl.edu/risk). Similar smart phone versions may be attained for Apple and Android smart phones

Summary for the Clinician

- Risk calculators can be obtained via the internet and as apps for Apple and Android smart phones.
- Current risk calculators use risk factors uncovered in the OHTS population, and thus risk calculator results are most applicable to patients who resemble the OHTS population in terms of age, IOP level, having an open angle and normal visual field, etc.
- Medical history, life expectancy, and other factors not included in the risk calculator are also important to take into account when deciding whether to initiate treatment in an ocular hypertensive.

23.3 Can I Screen for Glaucoma with a Risk Calculator?

Screening for glaucoma is a complex topic that depends on factors such as the prevalence of disease, the diagnostic precision of the screening test, and the efficiency of the screening program. Perhaps clinicians would consider a risk calculator as a screening tool in an unselected, general population. As stated above, one should only use the current risk calculators in patients with primary ocular hypertension. However, a risk calculator does include key information for case-finding of glaucoma; it requires one to carefully examine the optic disc, consider visual field testing, and check IOP. Perhaps risk calculators help clinicians systematically collect all important information (e.g. cup-to-disc ratio) when examining patients to prevent undiagnosed glaucoma and ocular hypertension.

Summary for the Clinician

- The current risk calculator was designed for patients with primary ocular hypertension, not for screening.
- The risk calculator includes risk factors that should be considered in general when deciding whether or not to treat a patient.

23.4 What Does It Mean to Me and My Patient If the Risk Score Is High?

One does not want to treat all ocular hypertension patients. One study [7] suggested a risk calculator value >10 % as a level of risk that is cost-effective for treatment of ocular hypertension. However, the provider and patient should consider all beneficial and adverse outcomes of the ocular hypotensive treatment. These may include the impact of early visual field loss and the daily administration of ocular hypotensive medications on quality of life. Clinicians also need to consider life expectancy of their patients. A young, healthy ocular hypertensive may have a higher likelihood of developing meaningful visual field loss over their lifetime when compared with a 75-year-old with the same ocular findings but with coronary artery disease and lung disease. A predictive equation spanning 5 years may be too short a time period to mediate this discrepancy. The eye care provider and patient should consider the results of a risk calculator as supplemental information to determine whether to recommend treatment.

Summary for the Clinician

- Risk calculator predictions only span a 5-year period of time and not a lifetime, therefore this information must still be interpreted by the treating provider taking into account patient lifespan, health status, and values.
- A 10 % or greater risk of developing glaucoma from ocular hypertension over 5 years is considered a cost-effective level at which to treat ocular hypertension.

References

1. Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. Am J Epidemiol. 1991;134:1102–10.
2. Mansberger SL. A risk calculator to determine the probability of glaucoma. J Glaucoma. 2004;13:345–7.
3. Gordon MO, Torri V, Miglior S, et al. Validated prediction model for the development of primary open-angle glaucoma in individuals with ocular hypertension. Ophthalmology. 2007;114:10–9.
4. Mansberger SL, Cioffi GA. The probability of glaucoma from ocular hypertension determined by ophthalmologists in comparison to a risk calculator. J Glaucoma. 2006;15:426–31.
5. Mansberger S, Patterson E. Risk calculators: evidence-based care of ocular hypertension and glaucoma patients. Ophthalmology: Glaucoma. Essentials in; 2006. p. 36–44.
6. De Moraes, et al. Invest Ophthalmol Vis Sci. 2012;53:2702–2707
7. Kymes SM, Kass MA, Anderson DR, Miller JP, Gordon MO. Management of ocular hypertension: a cost-effectiveness approach from the Ocular Hypertension Treatment Study. Am J Ophthalmol. 2006;141(6): 997–1008.

Medical Treatment: First-Line Agents, Monotherapy, and Combination Therapy

24

Eugenio A. Maul and Eugenio J. Maul

Core Messages

- Prostaglandin analogs are the most frequently used first-line agents for monotherapy to reduce intraocular pressure (IOP).
- Beta-blockers remain useful as a first-line agent.
- When monotherapy fails to reach the target IOP and the IOP reduction is less than 15 % a class switch should be instituted.
- α adrenergic agonists and carbonic anhydrase inhibitors can be used as first-line agents although they are infrequently chosen.
- Miotics are seldom used as first-line agents today.

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24.1 Are Medications Still a First-Line Treatment for Glaucoma?

Numerous multicenter randomized controlled trials (RCTs), the CNTGS, OHTS, EMGTS, and CIGTS, have demonstrated the benefit of decreasing IOP with medical therapy [7]. To date, medical therapy remains the standard of care for initial and follow-up treatment of open-angle glaucoma (OAG). In our clinic, approximately 70 % of patients under care have been treated exclusively with topical medication. IOP lowering should aim for a target pressure range [3]. Several factors have to be considered in determining target IOP including baseline IOP, disease severity, age, and other risk factors; however, recent RCTs have shown that the amount of IOP reduction from baseline is most important. A dramatic impact on disease progression was observed with a target IOP reduction of 35 % in CIGTS, in which only 10–12 % of patients progressed over 5 years. This is in contrast to 44 % of EMGTS patients progressing in the same time frame where mean IOP reduction obtained was 25 % from baseline [48].

There are several classes of glaucoma medications (see Table 24.1). When medically treating glaucoma, the goal should be to reach the target pressure with the least number of medications, at

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Table 24.1 Drug classes and individual medications

Class of medication	Drugs
Prostaglandin analogs	Latanoprost, travoprost, bimatoprost, tafluprost, unoprostone
β-adrenergic blockers	Timolol, levobunolol, carteolol, metipranolol, betaxolol
α-adrenergic agonists	Brimonidine, apraclonidine
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide, acetazolamide, methazolamide
Cholinergic agonists	Pilocarpine, carbachol, phospholine iodide, demecarium bromide

the lowest concentrations, and at the lowest frequency of administration. In chronic diseases, such as OAG, efficacy and safety of drugs are key elements; however, long-term tolerability, cost, and friendly dosing schedules are crucial to reassuring patient compliance in this asymptomatic and potentially blinding disease.

Summary for the Clinician

- Medications are standard of care as initial treatment for glaucoma.
- A target range should be established for each patient.
- The simplest, most effective drug regimen should be recommended.

24.2 Why Are Prostaglandin Analogs (PGAs) Today's First-Line Monotherapy?

In 1996, the first prostaglandin analog, latanoprost 0.005 %, was granted approval by the U.S. Food and Drug Administration (FDA). Later other preparations of this class were introduced, bimatoprost 0.03 % and 0.01 %, travoprost 0.004 %, unoprostone 0.15 %, and tafluprost 0.0015 %. PGAs are more potent IOP-lowering drugs than beta-blockers, and now are considered the gold standard initial treatment for OAG and ocular hypertension (OHTN). PGAs lower IOP 25–30 % from baseline, the highest IOP-lowering effect of a glaucoma drug to date [55]. PGAs also have the advantage of once daily dosing, preferably at evening time. Their effect lasts beyond 24 h [39]. Instructing patients to close their eyes after instillation in order to increase ocular contact time has not been shown to affect IOP reduction [41].

PGAs, except for unoprostone, increase uveoscleral outflow. Unoprostone was approved by the FDA in 2000 as a PGA analog; however, it is a synthetic docosanoid molecule that increases conventional outflow through the trabecular meshwork, lowers IOP 10–25 % from baseline, and has a shorter duration of action necessitating twice daily dosing [19]. Unoprostone was recently reintroduced to the US market and again removed. Branded Lumigan contains either bimatoprost 0.01 % or 0.03 %, respectively. The efficacies of these two concentrations are not significantly different. A 12-month comparison of IOP reduction showed a 29 % decrease from baseline with 0.01 % (5.2–7.8 mmHg decrease) and a 30 % drop with 0.03 % (5.6–8 mmHg) [34]. The recently introduced tafluprost 0.0015 % has shown IOP reductions of 7.1 mmHg or 29.6 % from baseline, similar to what is seen with other PGAs [54]. The horizon is opening for a new PGA, latanoprostene bunod (LBN), which may be more effective than latanoprost. After exposure to ocular esterases, LBN is cleaved into latanoprost acid, which improves uveo-scleral outflow, and butanediol mononitrate, a nitric oxide donating moiety, which improves conventional aqueous humor outflow. IOP lowering with LBN at day 28 was 8.9 mmHg compared to 7.8 mmHg with latanoprost from an equivalent baseline IOP [57].

Latanoprost, bimatoprost, and travoprost were found comparable in their ability to reduce IOP in OAG and OHTN. A difference in tolerability was the only observed difference between the three drugs, with latanoprost being tolerated best [49]. However, other studies have found differences in the efficacy between PGAs. Bimatoprost was found superior to latanoprost in a 6-month RCT, 69–82 % of patients achieved a 20 % IOP

decrease compared to 50–62 % with latanoprost [46]. In a 6-week multicenter RCT, IOP lowering was significantly greater with travoprost than with latanoprost—8.3 mmHg versus 7.5 mmHg, respectively with baseline IOPs around 24.5 mmHg [42]. More dramatic is the observation of efficacy of bimatoprost in latanoprost non-responders. Fifteen non-responders to latanoprost having an average baseline IOP of 24.8 mmHg after washout and 24.1 mmHg after latanoprost rechallenge lowered their IOP to 18 mmHg with bimatoprost 0.03 % [20]. The most important point for the clinician is the possibility that an individual patient who does not respond to one PGA agent may respond to another, and thus it is worth switching PGAs before advancing therapy. Another reason to switch within class is tolerability. Brand name products Lumigan LS with a lower concentration of bimatoprost 0.01 % and Travatan benzalkonium chloride (BAK) Free and Travatan Z, which are non-BAK preserved products, are all intended to improve tolerability and to avoid BAK side effects.

Summary for the Clinician

- PGAs have the most potent IOP-lowering effect of all topical drugs.
- There is a difference in tolerability between PGAs.
- Non-responders to one PGA can have a good response to another PGA, justifying a switch within class.
- Different preservatives are used with different PGAs.

24.3 Should Beta-Blockers (BB) Still Be Used as a First-Line Agent?

Timolol maleate was the most potent topical IOP-lowering drug introduced after pilocarpine and epinephrine years ago. Following its approval by the U.S. FDA in 1978, it was considered the gold standard initial treatment for nearly two decades until 1996 when the first PGA was granted FDA approval. However, this class of medication remains efficacious, tolerated, and cost effective. Also, it is used in many fixed combination products [12]. A number of different beta-blocker preparations were approved after timolol's introduction into the marketplace (see Table 24.2). The following history is an illustration of the continued utility of beta-blockers.

Table 24.2 Available beta-blocker agents

Nonselective beta-blockers
Timolol preparations: Timolol maleate 0.25 % and 0.50 %; preservative-free timolol 0.25 % and 0.50 %; timolol maleate gel-forming solution 0.5 %; timolol hemihydrate 0.25 % and 0.50 %
Levobunolol hydrochloride 0.25 and 0.50 %
Carteolol hydrochloride 1 %
Metipranolol hydrochloride 0.3 %
Selective beta-1 blocker
Betaxolol hydrochloride suspension 0.25 %

Case report: A patient was diagnosed with early primary open-angle glaucoma in our clinic (see Fig. 24.1). Her visual acuity was 20/20 in both eyes and IOPs were 34 and 27 mmHg, respectively. The optic disc in the right eye showed an inferior notch with a corresponding visual field defect (see Fig. 24.2). The optic disc and visual field in the left eye were within normal limits. After a short discussion and thorough medical history, the patient was started on timolol maleate 0.25 % twice daily in both eyes. One month later, IOPs were reduced by 52.9 % and 51.8 %, respectively, to 16 and 13 mmHg in the right and left eyes. IOP control was maintained for the rest of the patient's 2-year follow-up. As illustrated by this case, topical beta-blockers remain a reliable and effective therapy for elevated IOP and they can be considered for initial medical management of glaucoma.

BBs antagonize β1 and β2 receptors in the ciliary body's nonpigmented epithelium and thereby reduce secretion of aqueous humor, which in turn lowers IOP [44]. One drop of timolol maleate 0.25 % or 0.50 % has its peak effect 2 h following administration and may last for 24 h. Nonselective BBs

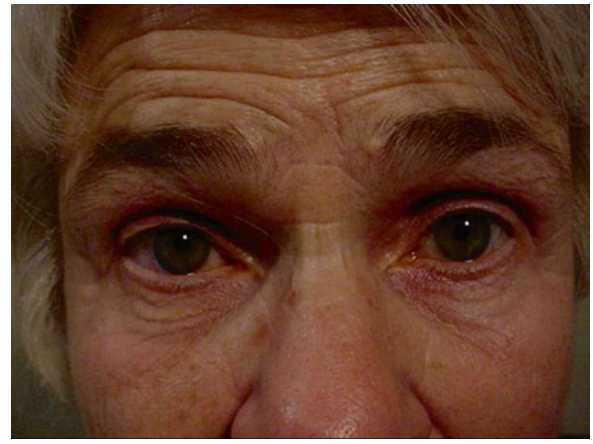

Fig. 24.1 A 68-year-old woman affected by glaucoma. Intraocular pressures at diagnosis were 34 mmHg in the right eye and 27 mmHg in the left eye. Timolol 0.25 % b.i.d. was initiated

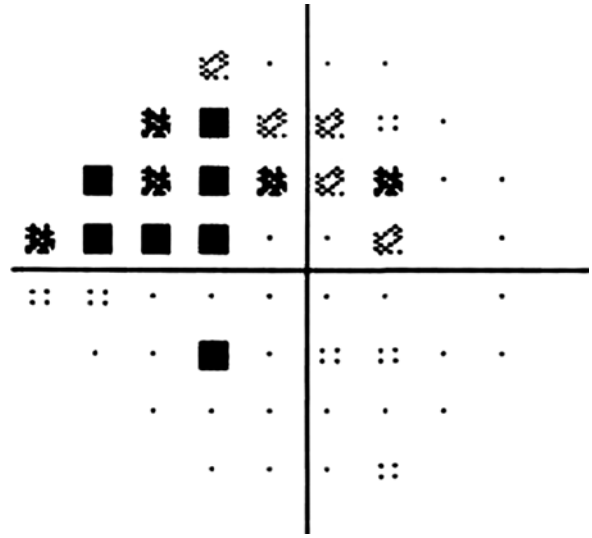

Fig. 24.2 The 24–2 SITA-standard pattern deviation of the right eye of the woman shown in Fig. 24.1, showing an early superior and nasal visual field defect

(Table 24.3) lower IOP 20–30 %. However, IOP reduction may be as high as 50 % and last greater than 24 h in certain individuals [58]. Among nonselective beta-blockers there are no differences in terms of IOP-lowering efficacy [60]. Carteolol has intrinsic α2 agonist sympathomimetic activity that does not interfere with the therapeutic benefits of its β-blocker action [2]. The selective β1 blocker, betaxolol, is less effective than timolol with reported IOP reduction between 16 and 20 % of baseline [17]. The advantage of selective β1 blockers is that they have less effect on the β2 receptors found predominantly in the

Table 24.3 Average additive intraocular pressure drop with a second agent

Beta blocker plus	
Prostaglandin analog	14–37 %
Carbonic anhydrase inhibitor	16–22 %
Alpha agonist	19 %
Miotic	6–17 %
Prostaglandin analog plus	
Beta blocker	12.3 %
Carbonic anhydrase inhibitor	19.7 %
Alpha agonist	9–23 %
Miotic	7.4 %

pulmonary system, making them more tolerable in patients with the potential for bronchospasm. Patients under treatment with systemic β-blockers may experience a reduced effect of topical administration and increased side effects [22].

The dramatic IOP reduction observed after initiation of timolol can be sustained in many patients. However, in up to 20 % of cases the initial IOP reduction can be lost within 2–3 weeks. This has been called "short-term escape," and most likely reflects an up regulation in the number of ocular β-receptors after initial complete blockade [6]. For this reason, it is recommended to wait at least 4 weeks following initiation of therapy before assessing IOP effect. In some patients, there is a phenomenon called "long-term drift" in which IOP control may be lost after many years of therapy, or even within months [6]. This drift may be the result of drug tolerance or progression of the trabecular meshwork outflow problems. In a 10-year follow-up of timolol-treated patients, 35 % needed additional therapy, laser, or surgery because of loss of control with timolol monotherapy [23].

There are two approaches to follow when initiating beta-blocker treatment. Generally, the lowest concentration (0.25 % vs. 0.5 %) and lowest frequency (once daily vs. twice daily) necessary should be used to avoid excess drug absorption and to minimize adverse effects.

Summary for the Clinician

- BBs are a fair choice as first-line agent due to good efficacy, good tolerability, and widely available generics.
- Nonselective BBs are more potent than selective BBs.
- There is both short-term escape and long-term drift with the use of BBs.
- BBs are less effective at night because there is naturally less aqueous production when patients are sleeping.
- Topical BB therapy may produce a smaller than expected IOP drop in patients under systemic treatment with BBs.

24.4 Are α Adrenergic Agonists Appropriate as a First-Line Therapy?

The selective α2 agonist brimonidine 0.2 % lowers IOP 20–23 %, which is less than what is seen with PGAs or nonselective BBs [8, 32]. Trough IOP is −4.5 mmHg, a 17 % reduction from baseline [55]. Lower efficacy and the recommended three times daily dosing makes this class less attractive as a first-line agent. However, if patients elect not to use a PGA or BB due to the side effect profiles or contraindications, brimonidine may be used dosed b.i.d. or t.i.d. Alphagan P is a branded brimonidine 0.1 % or 0.15 % that uses Purite as the preservative. This formulation replaced Alphagan 0.2 % which had BAK as the preservative. All formulations have similar daytime IOP-lowering effects [30, 33].

Summary for the Clinician

- α Adrenergic agonists are less potent than PGAs and BBs and require three times daily dosing for maximal efficacy.
- They can be used as first-line therapy, although they are not usually the first choice for monotherapy.

24.5 Are Carbonic Anhydrase Inhibitors Appropriate as First-Line Therapy?

Topical carbonic anhydrase inhibitors (CAIs) have fewer systemic adverse effects than oral CAIs, which has made it possible to incorporate this class of drugs into routine use for glaucoma treatment. Dorzolamide 2 % and brinzolamide 1 % are safe and well tolerated topical medications. The IOP-lowering effect of brinzolamide bid or tid are not significantly different (3.8–5.7 mmHg vs. 4.2–5.6 mmHg) from dorzolamide 2 % applied tid (−4.3 to −5.9 mmHg). Topical

CAIs reduce IOP by 18–25 % from baseline. They are less effective than PGAs and timolol maleate [52] and are generally used as adjunctive medication or in fixed combinations. In patients where timolol or PGAs cannot be used topical CAI may be used as primary agents. CAIs lower IOP at night time [40, 43].

Summary for the Clinician

- CAIs are less potent than PGAs and BBs and require three times daily dosing for maximal efficacy.
- They can be used as first-line therapy, although they are not usually the first choice for monotherapy.

24.6 Is it Still Appropriate to Use Miotics?

Miotics are seldom used today because more effective topical medications requiring less frequent administration and causing fewer side effects are available. Of 2775 patients receiving monotherapy in one series, only 21 were treated with miotics [61]. Pilocarpine, which increases trabecular outflow, remains useful in combination with beta-blockers and with prostaglandin analogs [1]. Its low cost makes it attractive when cost is an issue. Miotics are indicated in the management of some cases of acute angle-closure glaucoma, aphakic and pseudophakic glaucoma, and in presbyopic patients. They are contraindicated in uveitic or neovascular glaucoma.

Pilocarpine and other miotics are associated with many ocular side effects because of their effect on muscarinic cholinergic receptors present in the iris and ciliary body muscles. The indirect-acting miotics, phospholine iodide and demecarium bromide, act by inhibiting cholinesterase and they can affect systemic cholinesterase, which prolongs the effect of succinylcholine during general anesthesia. The following history is an example of when miotic may be useful.

Case history: A 70-year-old lady with OAG presented with IOP OD 28 and OS 39 mmHg. Treatment with timolol maleate 0.5 % bid and latanoprost 0.005 % qhs lowered her IOPs to 12 and 15 mmHg. The patient questioned the cost of treatment. Latanoprost was replaced by low cost pilocarpine 2 % bid, which was well tolerated despite miosis (Fig. 24.3). IOP measured 18 mmHg in both eyes on the timolol and pilocarpine combination, which was still a 40 % reduction from baseline.

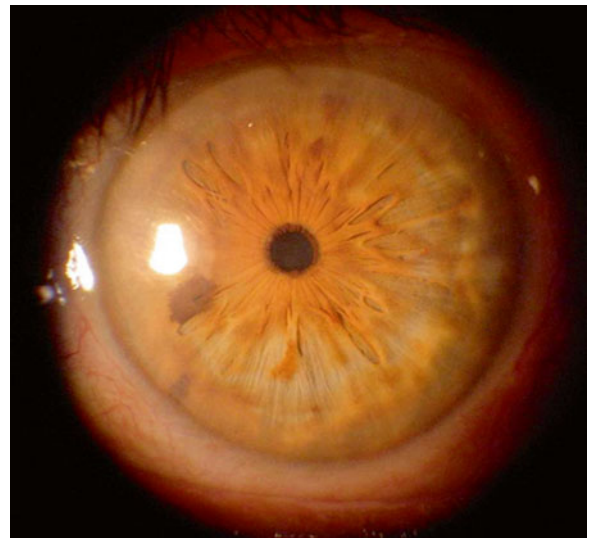

Fig. 24.3 Miosis observed in an eye with IOP controlled on timolol maleate bid and pilocarpine 2 % bid

Summary for the Clinician

- Despite their efficacy, miotics are seldom used today because of the availability of drugs with easier dosing regimens and fewer side effects.
- Miotics remain a useful medication when cost is an issue, especially in presbyopic patients.

24.7 If a Single Agent Does Not Provide Adequate IOP Lowering, Is It Better to Switch within the Same Class or to Another Class of Medication, or Is It Better to Add a Second Medication?

When IOP reduction is insufficient, it is important to understand the mechanism of action of each individual medication in order to decide how best to proceed with IOP lowering. When medically treating glaucoma, the goal should be to treat with the least number of medications, at the lowest concentrations, and at the lowest frequencies of administration, taking cost into account. Generally, monotherapy is instituted first. If target IOP is not reached with the first agent, a class switch can be tried first and then combination therapy with a second drug can be tried. If monotherapy reduces IOP yet fails to reach the target IOP, one should examine the percentage drop in IOP that *was* achieved to help determine whether or not the drug should be substituted or maintained with a drug addition. It is generally accepted that a 15 % or greater drop in IOP justifies continued use of the first drug with the addition of a second drug, instead of substitution. Combining medications is frequently necessary to lower IOP adequately. In the Ocular Hypertension Treatment Study, 49 % of patients in the treatment arm required two or more drugs to reach their individual IOP target [31]. In another study, the rate of non-responders at the 6th month of treatment, defined as an IOP reduction less than 15 % from baseline, was 26.4 % for timolol and 13.2 % for latanoprost [10]. In general, if a class of medication cannot produce at least a 15 % reduction in IOP it is better to switch to another class of medication before adding a second agent.

It is generally accepted that switching within a medication class adds little therapeutic effect, except possibly with the prostaglandin class of medications as discussed above in Sect. 24.2. Some studies have shown some patient subsets to be more responsive to one brand name drop than to another. This may justify switching PGAs in cases of insufficient response with the first PGA tried. However, it is important to keep in mind that the IOP-lowering effect of a PGA may not reach its maximal effect until 6–8 weeks of treatment, so decisions to switch should be reserved until after this trial period. Another exception is with beta blockers where switching from a selective β1 blocker (i.e. Betaxolol) to a nonselective beta blocker (i.e. timolol) generally results in a larger IOP reduction since the later are more potent at the expense of more systemic side effects. Switching between topical carbonic anhydrase inhibitors does not appear justified in terms of IOP reduction.

Summary for the Clinician

- Monotherapy should reduce IOP at least 15 % from baseline, otherwise a patient can be labeled a non-responder.
- If IOP reduction is less than 15 %, a class switch should be made, although sometimes switching from one prostaglandin to another prostaglandin can lead to greater IOP decrease.
- If IOP drops 15 % or more but the target pressure is not reached, a second medication should be combined with the initial therapy.

24.8 When Combining Topical Medications, Do Certain Combinations Work Better Together than Others?

There are no protocols for the order in which to add medications to each other. Beta-blockers were first-line agents for many years, but largely have been replaced by prostaglandin analogs. With either beta-blockers or prostaglandin analogs, one may expect that up to a quarter of patients will not experience an IOP drop greater than 15–20 % [10]. In these patients combination therapy may be necessary.

If a patient on beta-blocker monotherapy requires a second drug, combination therapy may begin with a fixed combination product, like timolol/dorzolamide or timolol/brimonidine in the United States or with timolol/latanoprost, timolol/travoprost, timolol/bimatoprost, or timolol/tafluprost outside of the United States. The addition of a separate prostaglandin analog nightly to a beta-blocker every morning is also effective [35] with an additional IOP-lowering effect between 14 and 37 % [25]. Use of the fixed timolol/dorzolamide formulation has been found to be equally efficacious to latanoprost alone [37] and to the timolol/latanoprost fixed combination [13]. Timolol and dorzolamide 2 % used together in a nonfixed combination causes an additional IOP reduction ranging from 16 to 22 % [11]. It has been suggested that the fixed combination CAI/beta-blocker may be more effective than individually combining drugs. Two additional mmHg of IOP lowering was seen when combined therapy was administered as a fixed combination [11]. Additional IOP lowering is also seen when parasympathomimetics (6–17 %) [1] and alpha2-agonists [36] are used with beta-blockers.

In patients on monotherapy with latanoprost, additive IOP effects are seen with beta-blockers (12.3 %), brimonidine (9.3 %), and dorzolamide (19.7 %) [47]. Combination with pilocarpine 2 % also produces an additional IOP reduction of 7.4 %. Conversely, when latanoprost was added to pilocarpine, the additional effect was 14.2 % [2]. When a second agent is needed in combination with a prostaglandin analog, consideration should first be given to a beta-blocker or topical CAI. The advantage of using a beta-blocker is the availability of fixed combinations in many parts of the world, which can lead to better compliance. However, the use of timolol twice daily and latanoprost once daily has been shown to further decrease IOP (on average 1.2 mmHg) than the fixed combination products. The advantage of using a CAI twice daily with a prostaglandin analog may be a stronger IOP-lowering effect [18, 28, 47]. Table 24.3 shows the average additive IOP drop with a second agent.

Summary for the Clinician

- Beta-blockers can be used in combination with any other available class of drug. Fixed combinations with CAIs may be slightly more effective than using the two medications separately.
- Prostaglandin analogs can also be used in combination with any other available class of drug. CAIs may offer a slight edge over beta-blockers.
- CAIs, but not BB or α agonists, are effective at night time.

24.9 What Are the Advantages of Fixed Combination Eye Drops?

Frequently, one medication is not sufficient to reach target pressures and a second or third bottle of medication must be added to a patient's regimen. Disadvantages of this multi-dosage approach include inconvenience and poor adherence. Long-term compliance with 2 or more drugs may be less than 40 % [50]. The efficacy (defined as reducing IOP 20 % or more from baseline) of a third drug may fall below 30 % [45]. Fixed combination drugs (FCs) combine

Table 24.4 Fixed combination drugs

Branded name	Drugs
Cosopt	dorzolamide 2 % + timolol maleate 0.5 %
Xalacom	Latanoprost 0.005 % + timolol maleate 0.5 %
Combigan	Brimonidine 0.2 %, + timolol maleate 0.5 %
Ganfort	Bimatoprost 0.03 % + timolol maleate 0.5 %
Duotrav	Travoprost 0.004 % + timolol maleate 0.5 %
Azarga	Brinzolamide 1 % + timolol maleate 0.5 %
Simbrinza	Brimonidine 0.2 % + brinzolamide 1 %
Krytantek Ofteno	Brimonidine 0.2 % + dorzolamide 2 % + timolol maleate 0.5 %
TAF/TIM	Tafluprost 0.0015 % + timolol maleate 0.5 %

two or more hypotensive agents in a single bottle. This reduces dosing frequency, which tends to improve adherence and reduce preservative exposure [4]. FCs generally offer equivalent efficacy compared to use of the separate individual components, with equivalent or superior tolerability. Studies also show that FCs can be more cost effective than nonfixed combinations [27].

Table 24.4 lists current FCs for the treatment of glaucoma. The efficacy of fixed combinations is generally that of the combined use of its components [12] except for dorzolamide/timolol fixed combination, which appears to have a stronger effect than using its components separately [11]. Branded TAF/TIM (a tafluprost 0.0015 % and timolol 0.5 % preservative-free fixed combination) reduced IOP 8.5 mmHg from a 25 mmHg baseline, similar to other PGA/timolol fixed combinations; however, it caused fewer superficial ocular side effects and less conjunctival hyperemia [26]. All FCs contain timolol maleate as one of their components except for the recently introduced brimonidine 0.2 % plus brinzolamide 1 % fixed combination. This FC is very efficacious with an IOP reduction of 26.7–36 % from baseline with twice daily dosing, and was found to have an equal IOP-lowering effect to its componenets dosed separately. It is approved for tid dosing [5, 21].

Summary for the Clinician

Advantages of fixed combination drugs include

- Easier dosing schedules,
- Reduced exposure to preservatives, and
- Equivalent efficacy to the separate use of their components.

24.10 What Are the Side Effects of Glaucoma Medications?

Safety and long-term tolerability are essential for successfully sustained glaucoma drug usage. Some drug classes pose potentially serious side effects for individual patients and should be avoided. Tolerability, in terms of eyelid and conjunctival irritation and allergy, must also be considered although these issues are frequently impossible to predict in the individual patient.

24.10.1 What Are the Side Effects of Prostaglandin Analogs?

Ocular side effects include conjunctival hyperemia, iris darkening, eyelash changes, periorbital and periocular skin changes. Cystoid macular edema, anterior chamber inflammation, and corneal pseudodendrites are considered potential and infrequent side effects of these drugs without clear evidence [9]. Systemic side effects are rare, and these drugs are extremely safe systemically.

Conjunctival hyperemia: Prostaglandin analogs may cause conjunctival hyperemia. When present, it is the earliest and most notorious side effect from the patient's viewpoint (see Fig. 24.4). The hyperemia is due to vasodilation and not from an allergic reaction, as seen with other drug classes. Latanoprost causes a mild conjunctival hyperemia, whereas hyperemia is more common and severe with bimatoprost and travoprost. A 12-week comparison study of latanoprost, travoprost, and bimatoprost observed redness in

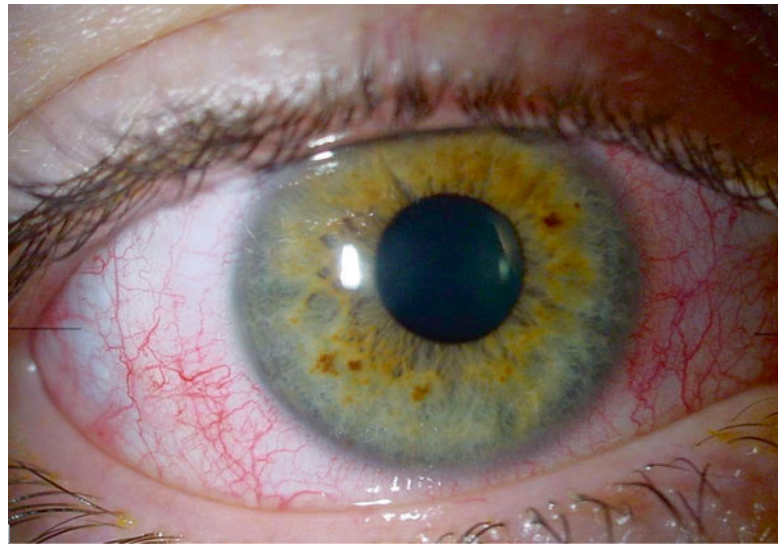

Fig. 24.4 Conjunctival hyperemia induced by treatment with a topical prostaglandin analog

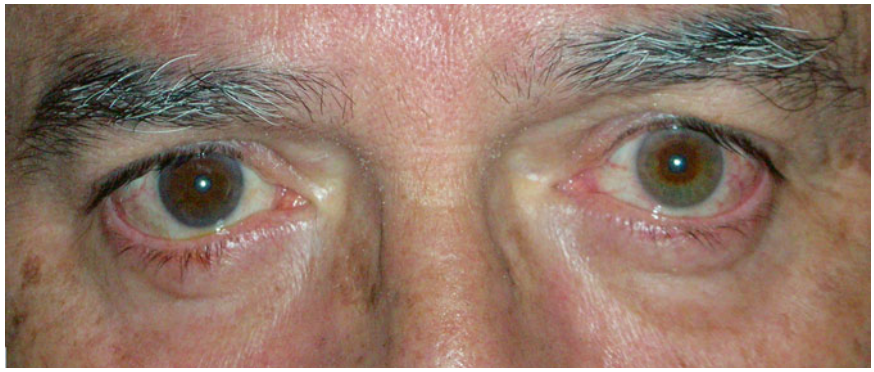

Fig. 24.5 Iris darkening of the right eye induced by unilateral therapy with prostaglandin analogs

16.6 %, 27.3 %, and 34.4 %, respectively. The hyperemia is shorter lived with latanoprost than with either bimatoprost or travoprost [49]. In order to reduce hyperemia and ocular irritation, bimatoprost was reformulated to a lower concentration of 0.01 % and travaprost was reformulated with a BAK-free preservative using polyquaternum 1 or SofZia® [4]. Also, preservative-free tafluprost is another option to protect the integrity of the ocular surface [54]. Although most in vitro studies demonstrate significant ocular toxicity from BAK and to a lesser degree from poliquad and Sofzia, evidence is not clear and consistent in clinical trials. The cost of these newer non-BAK formulations can exceed 5–10 times the cost of BAK preserved drugs [4].

Iris color darkening: This side effect occurred in 10 % of patients in a phase III study and was more frequent in eyes classified as green–brown, blue–gray–brown, or yellow-brown (see Fig 24.5). Blue/gray eyes did not change color [8, 56]. Some patients prefer not to expose themselves to the risk of iris color darkening and elect not to use PG analogs.

Eyelash changes: Increased length, darkening, thickening, and number of eyelashes have been observed with all PG analogs (see Fig 24.6). Some patients consider this beneficial.

Periorbital changes: Periorbital loss of fat causes deepening of the upper eyelid sulcus, involution

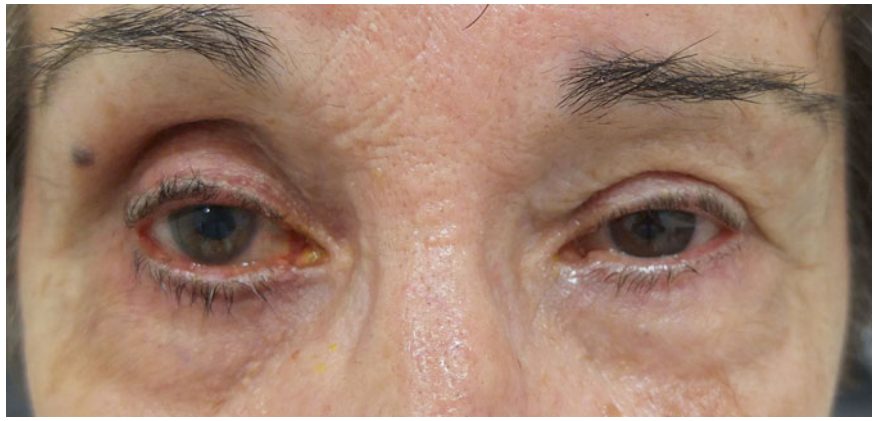

Fig. 24.6 Long-term unilateral treatment with PGA. Notice thicker, darker lashes on the right side. Also there is deepening of the superior eyelid sulcus due to orbital fat loss

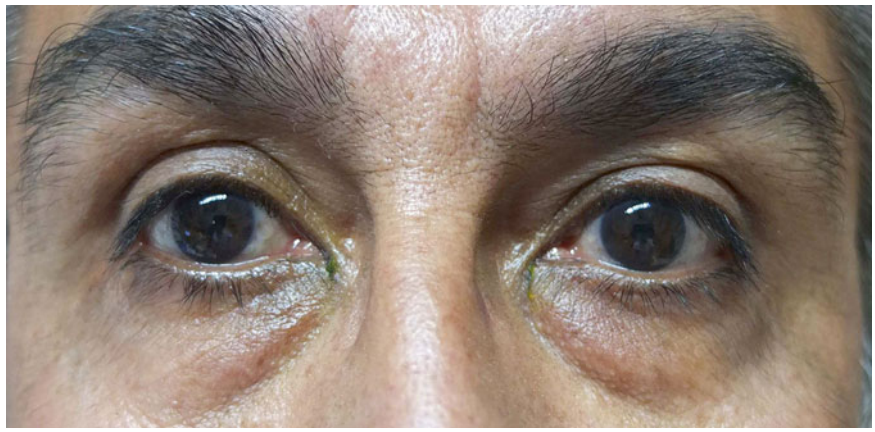

Fig 24.7 Eyelid skin darkening with use of prostaglandin analogs and increase in vellus hairs around eyes

of blepharochalasis and of lower eyelid fullness, and relative enophthalmos. Initially observed as a bimatoprost side effect, it was later observed with all PGAs (see Fig 24.6). A recent study found deepening of the upper eyelid sulcus in 60 %, 50 %, 24 %, and 18 % of patients treated with bimatoprost, travoprost, latanoprost, and tafluprost respectively [29, 51].

Periocular skin changes: Hyperpigmentation of the eyelids appears after 3–6 months of bimatoprost therapy and it may affect light and dark skinned patients (see Fig 24.7). It represents a harmless cosmetic problem and is fortunately reversible. Complete resolution has been observed between 3 and 12 months after discontinuation of bimatoprost. Another side effect of bimatoprost has been hypertrichosis of vellus hairs of the malar region, which may become prominent requiring epilation. It has also been observed to resolve 2 months after drug discontinuation [14, 24].

24.10.2 What Are the Side Effects of Beta-Blockers

Adverse ocular reactions are infrequent, and in general, beta-blockers are well tolerated when applied topically. Ocular tolerability with timolol maleate has not been surpassed by any topical

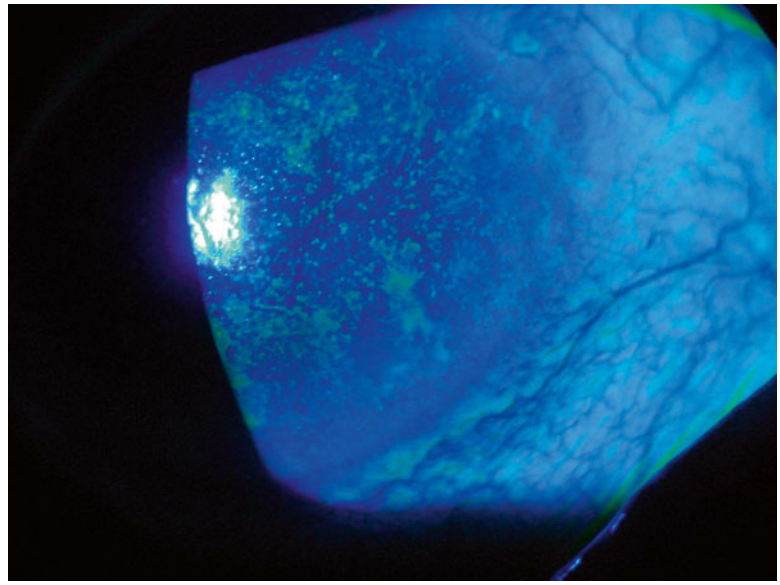

Fig. 24.8 Diffuse punctate keratitis probably induced by cumulative effect of benzalkonium chloride in multiple daily drops to control glaucoma awaiting surgical intervention

glaucoma medication since its approval. However, there are reports of ocular discomfort due to burning, hyperemia, toxic keratopathy, punctate keratopathy (see Fig 24.8), periocular contact dermatitis, and dry eye [2]. Chronic administration of BAK used as preservative in most beta-blocker solutions may play a role in ocular toxicity. Use of preservative-free timolol may help identify preservative as the source of local side effects. Timolol is available as a solution and in a gel-forming preparation. Gel-forming preparations allow longer permanence on the ocular surface for a sustained effect, and the once-daily administration can lead to fewer side effects. Gel-forming solution is also less likely to reach the nasolacrimal duct, lessening the potential for systemic side effects [59]. Gel-forming timolol may cause transient blurring, allergic conjunctivitis, and frosting of the lid margins and eyelashes. Metipranolol as manufactured in the United Kingdom was associated with granulomatous uveitis [16].

Systemic side effects of beta-blockers are significant. They are absorbed systemically via the nasolacrimal system by the nasal and oral mucosa, thus bypassing the first pass effect in the liver [15]. Direct access to the blood stream explains many systemic side effects and contralateral IOP lowering. Systemic side effects must be thoroughly searched for by a careful medical history since patients often overlook their eye drops as a potential cause of systemic symptoms. The majority of patients will not experience systemic adverse effects with topical BB use, but some patients can be exquisitely sensitive. Bradycardia, asthma, and a history of chronic obstructive pulmonary disease are contraindications for the use of beta-blockers. BB's may trigger airway disease in a previously undetected or asymptomatic patient. For this reason, patients with no contraindication for BB's must be questioned during follow-up visits for airway obstructive symptoms and other potential side effects. Betaxolol, a β_1 receptor blocker, has been successfully used in patients with pulmonary disease, but it is not entirely free of potential side effects [16]. Gentle closure of lacrimal puncta or eyelid closure for 2 min may decrease systemic absorption and the risk of significant adverse effects of beta-blockers.

Having listed all the potential negative side effects, if used in appropriate patients, the 35-year track record of beta-blockers still make them a safe and effective treatment option for treatment of elevated IOP [38].

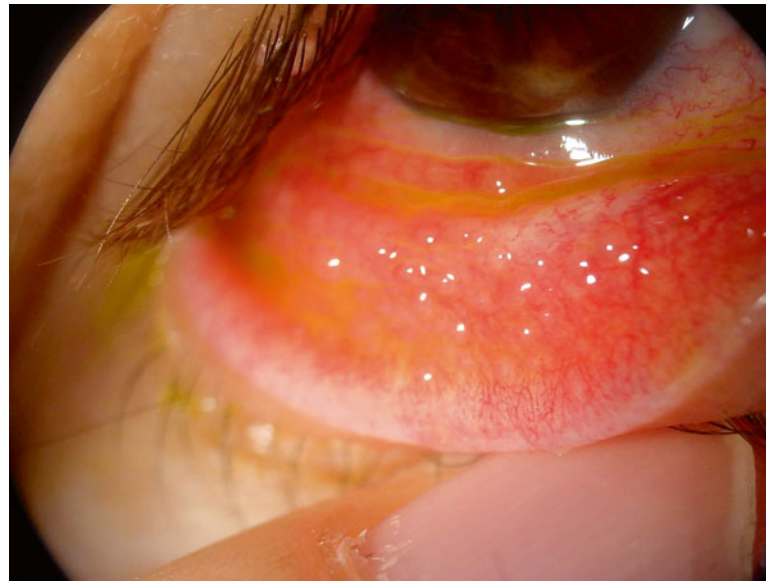

Fig. 24.9 Follicular conjunctivitis induced by use of topical brimonidine

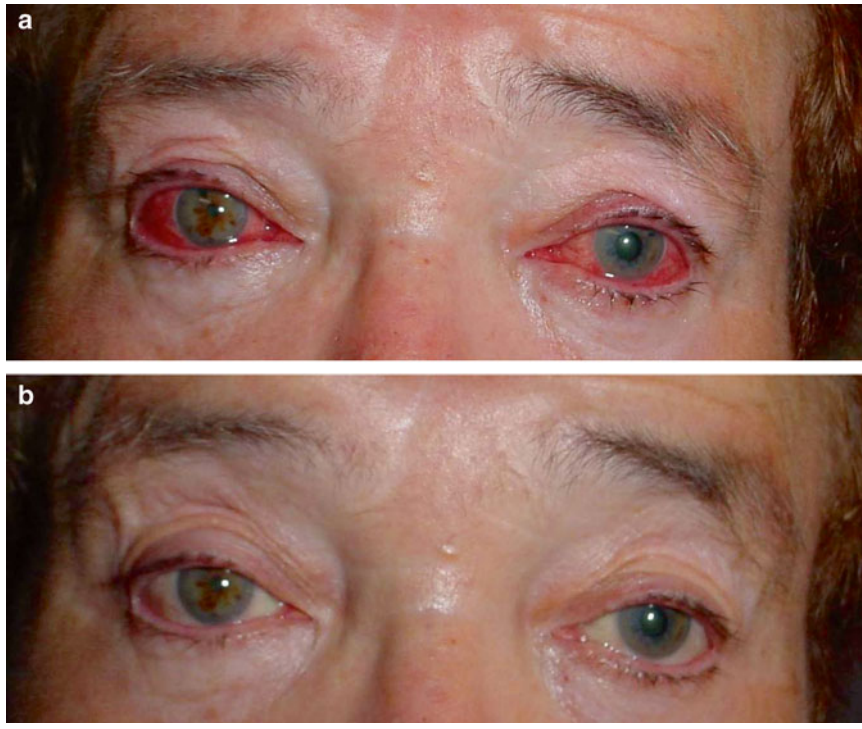

Fig. 24.10 (**a**) Bilateral follicular conjunctivitis induced by use of topical brimonidine. (**b**) Same patient seen 4 weeks after discontinuation of brimonidine

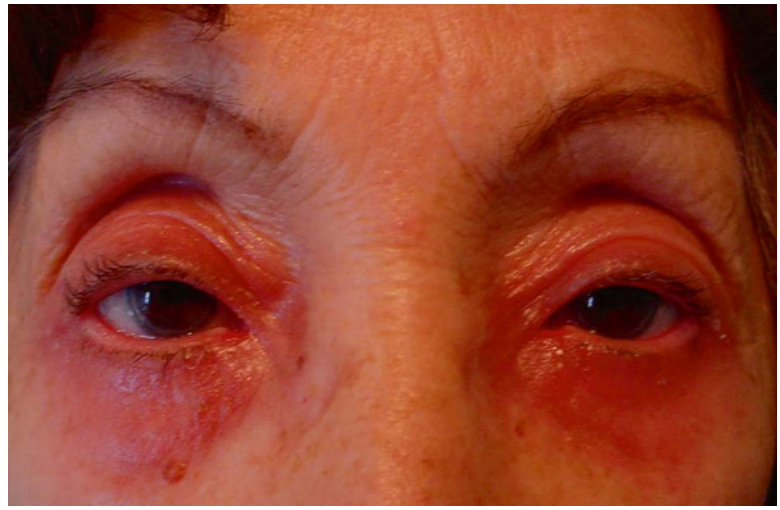

Fig 24.11 Periorbital dermatitis induced by topical carbonic anhydrase inhibitor

24.10.3 What Are the Side Effects of α Adrenergic Agonists?

Ocular side effects include ocular allergy, conjunctival follicles (see Fig 24.9), and periorbital dermatitis. Allergic reaction has been observed in up to 15 % in chronic treatment with brimonidine (see Fig 24.10). This figure is substantially lower than that observed with apraclonidine, in which allergy can occur in a third of patients [2]. In a 6-month controlled phase III study, ocular hyperemia and ocular allergic reactions affected 13.8 % of patients causing discontinuation of treatment [5].

Systemic side effects include bitter taste and dry mouth in up to 5 % of treated patients. Systemic adverse effects observed are generally not related to brimonidine, except in young children where it is contraindicated because of potentially life threatening side effects such as respiratory depression, apnea, bradycardia, and hypotension.

24.10.4 What Are the Side Effects of Carbonic Anhydrase Inhibitors?

Ocular side effects include allergic conjunctivitis and periorbital dermatitis (see Fig. 24.11). These are seen more frequently with topical dorzolamide than with topical brinzolamide. Burning and stinging has been observed more frequently with dorzolamide, which has a lower pH, and blurred vision is more often complained of with brinzolamide [52, 53]. Compromised corneas may decompensate with the use of topical CAI because of carbonic anhydrase that is inhibited within the cornea; this effect may be reversible. Fixed combination products produce reactions in a frequency similar to that caused by individual components [12].

Systemic side effects of topical CAI are markedly reduced compared with those observed with oral agents. Abnormal taste has been reported with dorzolamide and brinzolamide; however, this is usually minor and transient. Oral CAIs have substantial systemic side effects that limit their routine use in the management of glaucoma. See Chap. 26 for a full discussion of systemic CAI side effects.

Summary for the Clinician

- BBs are unmatched with regard to ocular tolerability, but systemic side effects must be watched for, especially in susceptible individuals.
- Prostaglandin analogs are extremely safe systemically, but do have ocular side effects.
- Topical CAI and α-2 adrenergic agonists may need to be discontinued for follicular conjunctivitis and periocular skin reactions.

References

1. Airaksinen PJ, Valkonen R, Stenborg T, et al. A double-masked study of timolol and pilocarpine combined. Am J Ophthalmol. 1987;104:587–90.
2. Allingham RR, Damji K, Freedman S, et al. Adrenergic receptor antagonists. In: Shield's Textbook of Glaucoma. Philadelphia: Lippincott Williams and Wilkins; 2005.
3. American Academy of Ophthalmology Preferred Practice Committee GP. Preferred practice pattern: primary open-angle glaucoma. In: Ophthalmology. Chicago: American Academy of Ophthalmology; 2010.
4. Anwar Z, Wellik SR, Galor A. Glaucoma therapy and ocular surface disease: current literature and recommendations. Curr Opin Ophthalmol. 2013;24:136–43.
5. Aung T, Laganovska G, Paredes TJH, et al. Twice-daily brinzolamide/brimonidine fixed combination versus brinzolamide or brimonidine in open-angle glaucoma or ocular hypertension. Ophthalmology. 2014;121:2348–55.
6. Boger III WP. Short term "escape" and long term "drift": the dissipation effects of the beta adrenergic agents. Surv Ophthalmol. 1983;28(Suppl):235–42.
7. Boland MV, Ervin AM, Friedman DS, et al. Comparative effectiveness of treatments for open angle glaucoma: a systematic review for the US Preventive Task Force. Ann Intern Med. 2013;158:271–9.
8. Camras CB, Wax MB, Ritch R, et al. Latanoprost treatment for glaucoma: effects of treating for 1 year and of switching from timolol. Am J Ophthalmol. 1998;126:390–9.
9. Camras CB. Safety and side-effects of latanoprost. In: Weinreb R, Kitazawa S, Ktieglstein GK, editors. Glaucoma in the 21st century. London: Mosby International Ltd; 2000.
10. Camras CB, Hedman K, US Latanoprost Study Group. Rate of response to latanoprost or timolol with ocular hypertension or glaucoma. J Glaucoma. 2003; 12:466–9.
11. Choudhri S, Wand M, Shields MB. A comparison of dorzolamide-timolol combination versus the concomitant drugs. Am J Ophthalmol. 2000;130:832–3.
12. Cox JA, Mollan SP, Bankasrt J, et al. Efficacy of antiglaucoma fixed combination therapy versus unfixed components in reducing intraocular pressure: a systematic review. Br J Ophthalmol. 2008;92: 729–34.
13. Cvenkel B, Stewart JA, Nelson LA, et al. Dorzolamide/timolol fixed combination versus latanoprost/timolol fixed combination in patients with primary open-angle glaucoma or ocular hypertension. Curr Eye Res. 2008;33:163–8.
14. Doshi M, Edward DP, Osmanovic S. Clinical course of bimatoprost-induced periocular skin changes in caucasians. Ophthalmology. 2006;113:1961–7.
15. Dunham CN, Spaide RF, Dunham G. The contralateral reduction of intraocular pressure by timolol. Br J Ophthalmol. 1994;78:38–40.
16. Fechtner RD. Beta blockers. In: Netland PA, Allen RC, editors. Glaucoma medical therapy principles and management. San Francisco: The Foundation of the American Academy of Ophthalmology; 1999.
17. Feghali JG, Kaufman PL. Decreased intraocular pressure in the hypertensive human eye with betaxolol, a β1—adrenergic antagonist. Am J Ophthalmol. 1985; 100:777–82.
18. Feldman RM, Tanna AP, Gross RL, et al. Comparison of the ocular hypotensive efficacy of adjunctive brimonidine 0.15 % or brinzolamide 1 % in combination with travoprost 0.004 %. Ophthalmology. 2007;114: 1248–54.
19. Fung DS, Whitson JT. An evidence-based review of unoprostone isopropyl ophthalmic solution 0.15 % for glaucoma: a place in therapy. Clin Ophthalmol. 2014; 8:543–54.
20. Gandolfi SA, Cimino L. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. Ophthalmology. 2003;110:609–14.
21. Gandolfi SA, Lim J, Sanseau AC, et al. Randomized trial of brinzolamide/brimonidine versus brinzolamide plus brimonidine for open-angle glaucoma or ocular hypertension. Adv Ther. 2014;31:1213–27.
22. Gieser SC, Juzych M, Robin AL, et al. Clinical pharmacology of adrenergic drugs. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas. St. Louis: Mosby; 1996.
23. Goethals M. Ten year follow-up of timolol-treated open angle glaucoma. Surv Ophthalmol. 1989;33 (Suppl):463–4.
24. Hart J, Shafranov G. Hypertrichosis of vellus hairs of the malar region after unilateral treatment with bimatoprost. Am J Ophthalmol. 2004;137:756–7.
25. Hejkal TW, Toris CB, Camras CB. Prostaglandin analogs. In: Netland PA, Allen RC, editors. Glaucoma medical therapy principles and management. San Francisco: The Foundation of the American Academy of Ophthalmology; 1999.
26. Holló G, Vuorinen J, Tuominen J, et al. Fixed-dose combination of tafluprost and timolol in the treatment of open-angle glaucoma and ocular hypertension: comparison with other fixed-combination products. Adv Ther. 2014;31:932–44.
27. Hommer A. Role of fixed combinations in the management of open-angle glaucoma. Expert Rev Pharmacoecon Outcomes Res. 2011;11:91–9.
28. Hommer A, Ganfort Investigators Group I. A double-masked, randomized, parallel comparison of a fixed combination of bimatoprost 0.03 %/timolol 0.5 % with non-fixed combination use in patients with glaucoma or ocular hipertensión. Eur J Ophthalmol. 2007;17:53–62.
29. Inoue K, Shiokawa M, Wakakura M, et al. Deepening of the upper eyelid sulcus caused by 5 types of prostaglandin analogs. J Glaucoma. 2013;22:626–31.
30. Cantor LB, Safyan E, Liu CC, et al. Brimonidine-purite 0.1 % versus brimonidine-purite 0.15 % twice daily in glaucoma or ocular hypertension: a 12-month randomized trial. Curr Med Res Opin. 2008;24:2035–43.
31. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized

trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701–13.
32. Katz LJ, The Brimonidine Study Group. Brimonidine Tartrate 0.2 % twice daily: 1-year results in glaucoma patients. Am J Ophthalmol. 1999;127:20–6.
33. Katz LJ. Twelve-month evaluation of brimonidine-purite versus brimonidine in patients with glaucoma or ocular hypertension. J Glaucoma. 2002;11: 119–26.
34. Katz LJ, Cohen JS, Batoosingh AL, et al. Twelve-month, randomized, controlled trial of bimatoprost 0.01 %, 0.0125 % and 0.03 % in patients with glaucoma or ocular hypertension. Am J Ophthalmol. 2010;149:661–71.e1.
35. Konstas AG, Nakos E, Tersis I, et al. A comparison of once daily morning vs evening dosing of concomitant latanoprost/timolol. Am J Ophthalmol. 2002;133: 753–7.
36. Konstas AG, Katsimpris IE, Kaltsos K, et al. Twenty-four-hour efficacy of the brimonidine/timolol fixed combination versus therapy with the unfixed components. Eye. 2008;22:1391–7.
37. Konstas AG, Kozobolis VP, Tsironi S, et al. Comparison of the 24 hour intraocular pressure-lowering effects of latanoprost and dorzolamide/timolol fixed combination after 2 and 6 months of treatment. Ophthalmology. 2008;115:99–103.
38. Lama PJ. Systemic adverse effects of beta-adrenergic blockers: an evidence based assessment. Am J Ophthalmol. 2002;134:749–60.
39. Liu JHK, Kripke D, Weinreb RN. Comparison of the nocturnal effects of once daily timolol and latanoprost on intraocular pressure. Am J Ophthalmol. 2004;138: 389–95.
40. Liu JH, Medeiros FA, Rigby SL, et al. Comparing diurnal and nocturnal effects of brinzolamide and timolol on intraocular pressure in patients receiving latanoprost monotherapy. Ophthalmology. 2009;116: 449–54.
41. Maul EA, Friedman DS, Quigley H, et al. Impact of eyelid closure on the intraocular pressure lowering effect of prostaglandins: a randomized controlled trial. Br J Ophthalmol. 2012;96:250–3.
42. Maul E, Carrasco FG, Costa VP, et al. A 6-week, multicenter, randomized, double masked, parallel-group study comparing travoprost 0.004 % to latanoprost 0.005 % followed by a 6-week open-label treatment with travoprost 0.004 %. Clin Ther. 2007;29:1915–23.
43. McCannel CA, Heinrich SR, Brubacker RF. Acetazolamide but not timolol lowers aqueous humor flow in sleeping humans. Graefes Arch Clin Exp Ophthalmol. 1992;230:513–20.
44. Mittag TW. Adrenergic and Dopaminergic drugs in glaucoma. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas. St. Louis: Mosby; 1996.
45. Neelakantan A, Vaishnav HD, Sherwood MB. Is addition of a third or fourth antiglaucoma medication effective? J Glaucoma. 2004;13:130–6.
46. Noecker RS, Dirks MS, Choplin NT, et al. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. Am J Ophthalmol. 2003;135:55–63.
47. O'Connor DJ, Martone JF, Mead A. Additive intraocular pressure lowering effect of various medications with latanoprost. Am J Ophthalmol. 2002;133:836–7.
48. Palmberg P. What is it about pressure that really matters in glaucoma? Ophthalmology. 2007;114:203–4.
49. Parrish RK, Palmberg P, Sheu WP. A comparison of latanoprost, bimatoprost, and travosprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study. Am J Ophthalmol. 2003;135:688–703.
50. Patel SC, Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. Ophthalmic Surg. 1995;26:233–6.
51. Peplinsky LS, Smith KA. Deepening of lid sulcus from topical bimatoprost therapy. Optom Vis Sci. 2004;81:574–7.
52. Silver LH, The Brinzolamide Primary Study Group. Clinical efficacy and safety of brinzolamide (Azopt TM), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol. 1998;126:400–8.
53. Stewart WC, Day DG, Stewart JA, et al. Short-term tolerability of dorzolamide 2 % and brinzolamide 1 % vs placebo in primary open-angle glaucoma and ocular hypertension subjects. Eye (Lond). 2004;18: 905–10.
54. Uusitalo H, Pillunat LE, Ropo A, et al. Efficacy and safety of tafluprost 0.0015 % eye drops in open-angle glaucoma and ocular hypertension: a 24-month results of a randomized, double-masked phase III study. Acta Ophthalmol. 2010;88:12–9.
55. Van der Valck R, Webers CAB, Schouten SAG, et al. Intraocular pressure-lowering effect of all commonly used glaucoma drugs. Ophthalmology. 2005;112: 1177–85.
56. Watson PG, The Latanoprost Study Group. Latanoprost. Two year's experience of its use in the United Kingdom. Ophthalmology. 1998;105:82–7.
57. Weinreb RN, Ong T, Sforzolini BS, et al. A randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005 % in the treatment of ocular hypertension and open angle glaucoma: the voyager study. Br J Ophthalmol. 2014;99:738–45. BJO online first published December 8, 2014 as 10-1136/bjophthalmol-2014-305908.
58. Zimmerman TJ, Kaufman HE. Timolol dose response and duration of action. Arch Ophthalmol. 1977;95: 605–7.
59. Zimmerman TJ, Shrir M, Nardin GF, et al. Therapeutic index of pilocarpine, carbachol and timolol with nasolacrimal occlusion. Am J Ophthalmol. 1992;114: 1–7.
60. Zimmerman TJ. Topical ophthalmic beta blockers: a comparative review. J Ocul Pharmacol. 1993;9: 373–84.
61. Zimmerman TJ, Stewart WC, The Latanoprost Axis Study Group. Intraocular pressure, safety, and quality of life in glaucoma patients switching to latanoprost from monotherapy treatments. J Ocul Pharmacol Ther. 2003;16:557–64.

Medical Treatment: The Pregnant and Nursing Woman

25

Thierry Zeyen and Greet Coppens

Core Messages

- There is no high level evidence for the fetal effects of medications used to treat glaucoma.
- Risks that topical and systemic medications pose to the fetus and neonate must be balanced against the risk of vision loss in the mother.
- All glaucoma medications should be avoided during the first trimester of pregnancy, if possible; systemic carbonic anhydrase inhibitors and prostaglandin analogs should be avoided absolutely.
- Some topical medications are deemed compatible with lactation by the American Academy of Pediatrics; however, caution should still be practiced.

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25.1 Which Glaucoma Medications Are Safe to Use in Pregnancy?

The management of glaucoma in pregnant women and during lactation is controversial, challenging, and full of conflicting advice [1, 2]. No clinical studies exist on the fetal effects of commonly used medications, and it is unlikely that trials will be performed. Trials to establish "safety and efficacy" of ophthalmic solutions are seldom performed in children or pregnant women because of medicolegal constraints, limited sample size, and low financial incentives to drug companies evaluating products in these populations [3]. Therefore, we must rely on the information gathered from case reports and animal studies.

Table 25.1 summarizes the U.S. FDA's categories of safety for medications during pregnancy. There are no glaucoma medications that fall into category A. Brimonidine is a category B drug, but it has been shown to cross the placenta and could potentially cause apnea in neonates if used through parturition. Beta blockers, CAIs, prostaglandin analogs, and parasympathomimetics are classified as category C. There have been reports of fetal complications from topical beta blockers; however, none have been seen with low dose timolol in gel formulation. Fetal complications have also been reported with systemic acetazolamide. There is only one case report of complications

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Table 25.1 Medication safety during pregnancy according to the U.S. FDA

Category A	Safety established using human studies
Category B	Presumed safety based on animal studies
Category C	Uncertain safety; no human studies; animal studies show adverse effect
Category D	Unsafe; evidence of risk that in certain clinical circumstances may be justifiable

with topical CAIs [4] in a neonate who also had low birth weight and impaired kidney function. Prostaglandins are known to stimulate uterine contraction and may cross the blood–placental barrier; prostaglandin analogs should be avoided during pregnancy to minimize risk of premature labor.

Childbearing plans should be addressed with all women of reproductive age who have glaucoma. The risks and benefits of glaucoma treatment to the fetus versus vision loss in the mother must be discussed. Also, it is probably a good practice to remind would-be mothers that a certain percentage of pregnancies will be anomalous by chance despite glaucoma treatment. As the greatest risk of medication to the developing fetus is in the first trimester, when organ systems develop, discontinuation of medications should occur prior to conception and through the first trimester. If a woman has advanced glaucoma and elevated pressures or if she is taking multiple medications, serious consideration should be given to surgery before conception. If the patient has early glaucoma or is only a suspect, stopping medications for a number of months should not pose any great risk to vision. Intraocular pressure (IOP) tends to decrease during pregnancy in healthy patients, especially during the second and third trimesters. However, in one retrospective review, almost 30 % of pregnant glaucoma patients experienced an *increase* in IOP during pregnancy [5].

If pregnancy is established and treatment is necessary, laser trabeculoplasty (LTP) is probably the best initial therapy and a good alternative to medication. If medications cannot be stopped then the use of beta blockers, cholinergics, topical CAIs, and alpha agonists can be continued. However, beta blockers and alpha agonists should be discontinued after the 8th month of pregnancy, to avoid beta- or alpha-blockade in the neonate (see Chap. 51 for effects in infants and children). Beta blockers have a long track record and are occasionally used by obstetricians for systemic hypertension during pregnancy. Timolol 0.1 % gel once daily is probably a safe option, due to the low dosage and low systemic absorption. If necessary it can be combined with dorzolamide or brinzolamide twice daily. Systemic CAIs are potentially teratogenic but topical CAIs appear to be safe.

Filtering surgery can be considered if glaucoma is progressive and an adequate IOP cannot be obtained with LTP or with the medications mentioned above. Peribulbar or sub-tenon lidocaine appears to be safe for the fetus. It is desirable to defer surgery until the second trimester of pregnancy to reduce the fetus' exposure to potentially teratogenic anesthetic agents. The patient should be positioned with the uterus displaced laterally so as to avoid aortic and vena caval compression by the gravid uterus [6]. Postoperatively, topical erythromycin and steroids in ointment or in drops using punctal occlusion are safe. Antimetabolites, such as 5-FU or mitomycin-C (MMC) should not be used on a pregnant woman for medicolegal reasons. Pregnant surgeons may also want to avoid handling these agents as occupational medicine does not allow the pregnant surgeons to handle MMC or 5-FU. Diode laser cyclodestruction can be a valuable alternative to filtering surgery [7]. Both the obstetrician and pediatrician should coordinate and provide the necessary care.

Questions about the safety of vaginal delivery in a woman with glaucoma occasionally arise. There is no literature which addresses these questions. The theoretical risks of vision loss from elevated eye pressure and decreased blood flow to the optic nerve during the pushing phase of labor should be discussed with the mother and may depend on the stage of the glaucoma. These concerns may also need to be addressed with the obstetrician.

Summary for the Clinician

- Evidence of glaucoma medication safety in pregnancy is largely derived from case reports and animal studies.
- Address glaucoma management prior to conception in women of childbearing age.
- IOP tends to decrease during pregnancy in healthy women, but has been reported to increase in up to one-third of pregnant glaucoma patients.
- Avoid prostaglandin analogs during pregnancy to minimize risk of premature labor.
- Avoid all medications during the first trimester of pregnancy to minimize possible teratogenic effects.
- In the second and third trimesters, beta blockers, alpha agonists, and miotics have been safely used but consider stopping the first two listed prior to childbirth to avoid complications in the newborn infant.
- If surgery is necessary during pregnancy, postpone it until the second trimester and avoid antimetabolite use.

25.2 What Medications Are Safe to Use in a Nursing Mother?

Again, a thorough discussion of the risks and benefits to the infant vs. those to the nursing mother should be discussed. *Beta blockers* are concentrated in breast milk and should be avoided while nursing, despite the American Academy of Pediatrics statement that beta blockers are compatible with lactation. It is unknown whether *alpha agonists* are excreted in human breast milk, but given the potential severity of side effects in an infant, they should be avoided during nursing. *Systemic CAIs* (acetazolamide, methazolamide) are considered compatible with lactation by the American Academy of Pediatrics, but given the unknown concentration found in breast milk, they should be used with caution or avoided in order to prevent hepatic and renal effects in the infant. *Topical CAIs* are generally considered safe and are approved by the American Academy of Pediatrics for use during lactation. *Prostaglandin analogs* are also considered to be reasonable choices in nursing mothers. The toxicity of *miotics* during lactation is unknown, with the exception of demecarium which should be avoided.

If *surgery* is offered to a nursing mother, the mother should be instructed to store breast milk ahead of the surgery and the operation should be timed immediately after nursing to avoid significant anesthetic concentrations in breast milk. Care should always be coordinated with the pediatrician, and the mother should be instructed on the signs/symptoms of medication side effects on her nursing child.

Summary for the Clinician

- Risks of medication to the infant must be weighed against the risks of not using medications to the mother.
- Beta blockers are concentrated in breast milk and should be avoided.
- Alpha agonists should be avoided since their excretion into human breast milk is unknown.
- Systemic CAIs should be used with caution or avoided all together to be safe.
- Topical CAIs, prostaglandins, and miotics are reasonable choices during lactation.
- If surgery is planned, breast milk should be stored in order to have milk unaffected by anesthetic agents.

References

1. Coleman AL, Mosaed S, Kamal D. Medical therapy in pregnancy. J Glaucoma. 2005;14:414–6.
2. Johnson SM, Martinez M, Freedman S. Management of glaucoma in pregnancy and lactation. Surv Ophthalmol. 2001;45:449–54.

3. Wallace DK, Steinkuller PG. Ocular medications in children. Clin Pediatr. 1998;37:645–52.
4. Morris S, Geh V, Nischal K. Topical dorzolamide and metabolic acidosis in a neonate. Br J Ophthalmol. 2003;87:1052–3.
5. Brauner SC, Chen TC, Hutchinson T. The course of glaucoma during pregnancy: a retrospective case series. Arch Ophthalmol. 2006;296:1284–5.
6. Melnick DM, Wahl WL, Dalton VK. Management of general surgical problems in the pregnant patient. Am J Surg. 2004;187:170–80.
7. Wertheim M, Broadway DC. Cyclodiode laser therapy to control intraocular pressure during pregnancy. Br J Ophthalmol. 2002;86:1318–9.

Medical Treatment: Carbonic Anhydrase Inhibitors

26

Simon K. Law

Core Messages

- Oral carbonic anhydrase inhibitors (CAIs) remain a useful choice for intraocular pressure (IOP) lowering.
- CAI dosing must be titrated to the individual.
- CAIs have many potential effects on human physiology and can cause serious complications or even death.
- Systemic CAIs are contraindicated in pregnancy.
- Methazolamide has a better pharmacologic profile than acetazolamide; however, acetazolamide may lower IOP more quickly.

26.1 Are Oral Carbonic Anhydrase Inhibitors Still to Be Used Now That There Are Numerous Effective Topical Medications?

Oral carbonic anhydrase inhibitors (CAIs) were introduced half a century ago for the treatment of glaucoma. Although their use in glaucoma care has been replaced largely by topical therapy, they are still an important therapeutic option in acute situations when topical therapy does not reduce intraocular pressure (IOP) adequately, as a last resort in patients who cannot tolerate topical therapy, or when surgery needs to be delayed or is contraindicated. Therefore, ophthalmologists should remain familiar with the pharmacology of CAIs.

Summary for the Clinician

- Oral CAIs remain useful.
- Ophthalmologists should remain familiar with CAI pharmacology.

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26.2 How Should Oral CAIs Be Dosed?

The ciliary body epithelium's formation of bicarbonate is linked with sodium transport and aqueous secretion. Accumulation of posterior chamber bicarbonate and the subsequent aqueous secretion is inhibited by CAIs. In therapeutic doses, CAIs can reduce up to 50 % of aqueous production and are highly effective for the reduction of IOP in acute situations [1]. For example, if a systemic CAI is given to a patient with an IOP of 40 mmHg (receiving no other ocular hypotensive therapy), the CAI will reduce the outflow pressure of 30 mmHg by 50 % and achieve an IOP of 25 mmHg [2]:

Pretreatment IOP	=40 mmHg
Episcleral venous pressure (EVP)	=10 mmHg
Outflow pressure	=IOP (40) − EVP (10) = 30 mmHg
Posttreatment IOP	=Outflow pressure × 50 % + EVP
	=30 mmHg × 50 % + 10 mmHg
	=25 mmHg

Maximum IOP reduction usually occurs within 2–4 h following oral administration and may last for 6–8 h. When given intravenously, IOP reduction can be observed within 2 min, with a peak effect noted in 10–15 min.

Excess carbonic anhydrase is present in the ciliary processes. It is calculated that 100 times as much enzyme as it is needed for the production of aqueous is present, and therefore the enzyme must be more than 99 % inhibited so as to significantly reduce aqueous flow [1]. However, the maximum CAI dose may not be necessary in every patient because of individual differences in absorption, excretion, metabolism, toxicity, and tolerability. In a nonacute situation, one can start oral CAIs at low doses, such as 25–50 mg of methazolamide twice daily or 125 mg acetazolamide four times daily. The maximum dose is 150 mg methazolamide twice daily, 250 mg acetazolamide tablets four times daily, or 500 mg sustained release acetazolamide capsule twice daily. In acute situations in the clinic, where an urgent reduction of IOP is desirable, usually a single oral dose of 500 mg acetazolamide (i.e., two 250 mg tablets) is administered. In these situations, regular acetazolamide is preferable over the sustained release acetazolamide sequel because a quick therapeutic dose is needed to reduce the IOP on an urgent basis.

Summary for the Clinician

- Individual patients will have different absorption, excretion, metabolism, and side effects with CAIs, and so doses should be individually titrated.
- Start with low doses—methazolamide 25–50 mg b.i.d. or acetazolamide 125 mg q.i.d.
- Maximum dosages are methazolamide 150 mg b.i.d., acetazolamide 250 mg tablets q.i.d., or acetazolamide 500 mg sequel capsule b.i.d.
- In acute situations, intravenous acetazolamide 500 mg can be given with an expected peak effect within 15 min or oral acetazolamide tablets can be given with an expected peak effect in 2–4 h.

26.3 What Are the Toxic Effects of Systemic CAIs?

Commonly reported side effects that may occur shortly after starting systemic CAIs are paresthesias, numbness, and tingling sensations in the hands, feet, and lips, malaise, somnolence, confusion, anorexia, nausea, abdominal discomfort, and an unpleasant taste in the mouth or poor tolerance to carbonated beverages [3]. Some of these side effects are associated with the metabolic acidosis that develops with CAIs or with the inhibitory action of carbonic anhydrase in the central nervous system and gastric mucosa. Reducing CAI dose can reduce these side effects.

The renal *metabolic acidosis* that develops with systemic CAIs may have serious side effects

in children or patients with diabetes mellitus, hepatic insufficiency, renal failure, or chronic obstructive pulmonary disease, and their use in these patients is relatively contraindicated. Metabolic acidosis develops when carbonic anhydrase is inhibited in the kidneys so that bicarbonate is lost in the urine. This loss of bicarbonate alkalinizes the urine, which in turn leads to increased reabsorption of ammonia, a factor to consider in patients with hepatic insufficiency who can then develop hepatic encephalopathy because of increased ammonia levels. CAI-induced metabolic acidosis may exacerbate ketoacidosis in patients with poor control of diabetes or in patients with a preexisting respiratory acidosis. Respiratory acidosis may also be induced in patients with severe chronic pulmonary disease by impairment of carbon dioxide transfer from the pulmonary vasculature to the alveoli in the presence of CAIs [1–3]. In patients with renal failure, the excretion of acetazolamide decreases so that doses must be adjusted for individual creatinine clearance. Patients on hemodialysis for renal failure can use CAIs, but the dose must be dramatically reduced. Although methazolamide is primarily metabolized by the liver, making kidney function less important in determining the dosage, electrolyte imbalance and severe acidosis may still occur in patients with poor renal function.

In healthy patients, *hypokalemia* and metabolic acidosis following the initiation of CAIs tend to be self-limited problems. However, hypokalemia may increase in severity if patients are taking other diuretics, steroids, or adrenocorticotropic hormone (ACTH), or when severe cirrhosis is present. Digitalis toxicity increases in the presence of hypokalemia; therefore, patients on digitalis who have poor renal or liver function, or who are taking other diuretics or steroids concurrently, should have their potassium level monitored periodically [2, 3]. A prudent practice is to fully inform a patient's primary physician about the systemic or topical ocular medications we prescribe to our glaucoma patients, especially those with comorbid conditions and on multiple systemic medications.

Kidney stone formation is not uncommon in patients chronically using systemic CAIs. The exact incidence of renal lithiasis due to CAIs is not well reported, although between 0 and 15 % has been seen after years of use [4, 5]. The stones are usually composed of calcium phosphate, due to the metabolic acidosis and resulting low levels of urinary citrate and high levels of urinary calcium. Ordinarily, urinary citrate forms a soluble complex with calcium, which can otherwise precipitate as an insoluble salt. The risk of kidney stone formation is lower with methazolamide than with acetazolamide. One retrospective case–control series reported the incidence of stones to be 11 times higher in patients using acetazolamide. Continued use after occurrence of a stone was associated with a high risk of recurrent stone formation. However, a history of spontaneous stone formation more than 5 years prior to acetazolamide therapy did not appear to be associated with an increased risk [6]. Very low serum levels of CAI are seen with topical application, and thus far no reports of kidney stones have been reported with their use [3].

All CAIs are members of the sulfonamide family, but CAIs do not contain the structural features that are responsible for the immunological reactions in sulfonamide antibiotics. These features include the N1 heterocyclic ring that is believed to be the immunologic determinant of type I immediate hypersensitivity reactions and reactive metabolites formed at the N4 amino nitrogen responsible for non-type I hypersensitivity responses to sulfonamide antibiotics. Therefore, cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamide-containing drugs is unlikely. However, a T-cell-mediated immune response to the parent sulfonamide structure appears to be responsible for hypersensitivity reactions in a small subset of patients. Thus, cross-reactivity remains possible. [7] The most severe form of manifest allergy is Stevens–Johnson syndrome, which can be fatal. It has been recognized that many patients report an allergy to sulfa that is not truly an allergic reaction, but rather a side effect, such as nausea [8]. If systemic CAI is urgently needed, it is worth exploring in depth the kind of reaction the patient previously experienced. It is prudent to instruct patients to report any rashes that break out on the body or angioedema after initiation of CAIs.

Aplastic anemia is a rare but potentially fatal idiosyncratic reaction to CAIs. Some patients may develop isolated neutropenia, thrombocytopenia, or pancytopenia that can recover uneventfully [9]. Routinely obtaining complete blood counts (CBC) are not predictive of this idiosyncratic reaction, which is very rare and not dose related, and therefore, routine CBCs are not recommended. However, patients can be alerted to report unusual epistaxis, bruising, or bleeding of the gums, as possible early signs of thrombocytopenia. There have been no reports of Stevens–Johnson syndrome or blood dyscrasias following use of topical CAIs [3]. However, given that systemic absorption occurs, it is recommended to discuss these possible side effects with patients when initiating topical therapy.

Summary for the Clinician

- Metabolic acidosis and hypokalemia can occur with systemic CAI use. Great caution is advised when prescribing CAIs to patients with poor renal or liver function, COPD, poorly controlled diabetes mellitus, and in those taking other diuretics, digitalis, steroid, or ACTH concurrently. Routinely checking bicarbonate and potassium levels in these patients is prudent.
- Dosing must be adjusted for creatinine clearance in renal insufficiency.
- Hepatic encephalopathy may occur in patients with hepatic insufficiency taking CAIs.
- Nephrolithiasis may occur and the risk is greater with acetazolamide.
- Severe allergic reactions, such as Stevens–Johnson syndrome, may occur.
- Aplastic anemia, a rare but potentially fatal idiosyncratic reaction to CAI, may occur. However, routine measurement of the CBC is not recommended.

26.4 Can CAIs Be Used in Pregnant Women or Pediatric Patients?

Both acetazolamide and methazolamide are classified by the U.S. Federal Drug Agency as category C drugs (meaning that studies in animals have indicated adverse effects to the fetus while no controlled studies in women are available, or neither human nor animal studies are available; the drug should only be given if the potential benefit outweighs risk to fetus). Forelimb deformity has been seen in the offspring of animals given acetazolamide. Sacrococcygeal teratoma and transient renal tubular acidosis in the neonates of women given acetazolamide has also been reported [10, 11]. Systemic CAIs are contraindicated in pregnant women and should be avoided by women of childbearing age who intend to become pregnant. Small amounts of acetazolamide have also been found in breast milk, so nursing mothers should avoid this medication. No teratogenic adverse effects have been reported with topical CAIs; however, there are no studies on their use in pregnant women.

Pediatric doses of systemic CAI are calculated according to body weight. The maximum dose for acetazolamide is 10–15 mg/kg/day divided three to four times daily.

It is recommended that chronic systemic CAI use be avoided or limited to very short periods of time because of the metabolic acidosis that occurs. Growth retardation has been reported in young children (1–6-years-old) receiving long-term CAI therapy for seizure disorders (mean duration of use, 3.5 years) due to metabolic acidosis. Children with chronic metabolic acidosis due to renal tubular disorders and diabetic ketoacidosis have also shown stunted growth [12].

Summary for the Clinician

- Systemic CAIs are contraindicated in pregnancy.
- Contraception is advised if used in women of childbearing age.

- Systemic CAIs should be avoided in children or used only for short periods of time.
- Growth retardation due to metabolic acidosis has been reported in children receiving long-term CAI therapy.

26.5 Can CAIs Be Used in Patients with Sickle Cell Anemia?

Metabolic acidosis increases the chances of red blood cell (RBC) sickling in patients with sickle cell anemia and sickle cell trait. In sickle cell patients with traumatic hyphema, IOP can often be very high, and given that decreased microvascular perfusion can make their optic nerve heads more susceptible to IOP damage, the use of systemic CAIs is often entertained. Sickling of RBCs can make it more difficult for them to pass through the trabecular meshwork, and it can also precipitate a systemic crisis. Use of systemic CAI in patients with sickle cell anemia or trait should be with caution and full discussion of risks.

Summary for the Clinician

- Metabolic acidosis increases the chance of RBC sickling in patients with sickle cell anemia.

26.6 How Does Acetazolamide Differ from Methazolamide?

The two oral CAIs commercially available are acetazolamide and methazolamide. Acetazolamide 250 mg and methazolamide 50 mg equivalently inhibit carbonic anhydrase. However, the greater metabolic acidosis associated with acetazolamide can result in a slightly lower IOP than seen with methazolamide for unknown reasons. Since methazolamide is less bound to plasma protein, a relatively lower dose is needed to produce therapeutic levels of carbonic anhydrase enzyme inhibition within the ciliary processes. Because of the excessive concentration of enzyme within the kidney, renal effects of bicarbonate loss from carbonic anhydrase inhibition may be avoided with a moderate dose of methazolamide. Theoretically, methazolamide has other pharmacological advantages over acetazolamide, such as better gastric absorption and easier access into ocular tissue due to a more favorable partition coefficient. It also has a longer duration of action (half-life equals 14 h or approximately double the half-life of acetazolamide) so that it can be administered twice daily [13]. Acetazolamide is available in a sustained-release (500 mg) form used twice daily. Both acetazolamide and methazolamide are well absorbed after oral administration. Acetazolamide is excreted as an intact drug by the kidney, whereas methazolamide is metabolized by the liver (only 25 % is excreted by the kidney); therefore, the dosage of methazolamide may not have to be adjusted in patients with renal insufficiency [1, 2]. For acute situations, where rapid IOP lowering is desired, the longer onset of action seen with methazolamide makes the drug less useful than acetazolamide.

Summary for the Clinician

- Methazolamide is better tolerated than acetazolamide.
- Methazolamide is less likely to cause a metabolic acidosis.
- Methazolamide is less likely to cause nephrolithiasis.
- Acetazolamide has a faster onset of action.
- A greater metabolic acidosis caused by acetazolamide provides additional IOP reduction.

26.7 Are Systemic and Topical CAI Effects Additive?

Oral CAIs can achieve a lower IOP than topical CAIs. Two proposed reasons may account for the stronger hypotensive effect of systemic CAIs. One, the metabolic acidosis induced by oral CAIs may independently lower IOP. The mechanism for this is unknown. Secondly, in addition to inhibition of carbonic anhydrase isozyme II, which is primarily responsible for aqueous humor production, there may be inhibition of other isozymes that contribute to aqueous production [14, 15]. However, the hypotensive effects of topical and oral CAIs are probably not additive [16]. Therefore, concomitant use of a therapeutic dose of topical and systemic CAI is not warranted. However, individual variation may occur. Patients may be using more than one topical medication so that the topical bioavailability of the drug may be lowered by a washout effect. In patients on suboptimal doses of oral CAI, topical CAI may have an additional effect.

Summary for the Clinician

- Oral CAIs may have a stronger hypotensive effect than topical CAIs.
- Generally, use of systemic and topical CAIs together is probably not warranted.
- Topical CAI may supplement the IOP reducing effect of systemic CAI when patients are on less than a full therapeutic dose of oral CAI.

References

1. Gabelt BT, Kaufman PL. Aqueous humor hydrodynamics. In: Kaufman PJ, Alm A, editors. Adler's physiology of the eye clinical application. 10th ed. St Louis: Mosby; 2003. p. 238–42.
2. Law SK, Caprioli. Medical therapy of glaucoma. In: Tasman W, Jaeger EA, editors. Duane's clinical ophthalmology, chapter 56. Philadelphia: Lippincott Williams & Wilkins; 2008.
3. Fraunfelder FT, Fraunfelder FW, editors. Drug-induced ocular side effects. Boston: Butterworth-Heinemann; 2001.
4. Katayama F, Miura H, Takanashi S. Long term effectiveness and side effects of acetazolamide as an adjunctive to other anticonvulsants in the treatment of refractory epilepsies. Brain Dev. 2002;24:150–4.
5. Tawil R, Moxley TR, Griggs RC. Acetazolamide-induced nephrolithiasis: implications for neuromuscular disorders. Neurology. 1993;43:1105–6.
6. Kass MA, Kolker AD, Gordon M, et al. Acetazolamide and urolithiasis. Ophthalmology. 1981;88:261–5.
7. Brackett CC, Harleen S, Block JH. Likelihood and mechanisms of cross-allergenicity between sulfonamide antibiotics and other drugs containing a sulfonamide functional group. Pharmacotherapy. 2004;24:856–70.
8. Lee AG, Anderson R, Kardon RH, et al. Presumed "sulfa allergy" in patients with intracranial hypertension treated with acetazolamide or furosemide: cross reactivity, myth, or reality? Am J Ophthalmol. 2004;138:114–8.
9. Zimran A, Beutler E. Can the risk of acetazolamide-induced aplastic anemia be decreased by periodic monitoring of blood cell counts? Am J Ophthalmol. 1987;104:654–8.
10. Maren TH, Ellison AC. The teratological effect of certain thiadiazoles related to acetazolamide, with a note on sulfanilamide and thiazide diuretics. Johns Hopkins Med J. 1972;130:95–104.
11. Brauner SC, Chen TC, Hutchinson BT, et al. The course of glaucoma during pregnancy. Arch Ophthalmol. 2006;124:1089–94.
12. Futagi Y, Otani K, Abe J. Growth suppression in children receiving acetazolamide with antiepileptic drugs. Pediatr Neurol. 1996;15:323–6.
13. Maren TH, Haywood JR, Chapman SK, et al. The pharmacology of methazolamide in relation to the treatment of glaucoma. Invest Ophthalmol Vis Sci. 1977;16:730–42.
14. Maus TL, Larsson LI, McLaren JW, et al. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. Arch Ophthalmol. 1997;115:45–9.
15. Hutzelmann JE, Polis AB, Michael AJ, et al. A comparison of the efficacy and tolerability of dorzolamide and acetazolamide as adjunctive therapy to timolol. Acta Ophthalmol Scand. 1998;76:717–22.
16. Tosenberg LF, Krupin T, Tang LQ, et al. Combination of systemic acetazolamide and topical dorzolamide in reducing intraocular pressure and aqueous humor formation. Ophthalmology. 1998;105:88–92.

Medical Treatment: Osmotic Agents

27

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Core Messages

- Intravenous mannitol and oral glycerin (glycerol) can be used for the rapid reduction of elevated intraocular pressure (IOP) in emergency situations.
- Hyperosmotics can be used to lower IOP before surgery so as to minimize certain intraoperative and postoperative complications that are associated with rapid reductions of very high IOP.
- Hyperosmotics should be avoided in patients with cardiac, pulmonary, or renal dysfunction.
- Oral glycerin should be avoided in diabetics.

27.1 When Using Hyperosmotics Agents, What Is a Typical Dose for Acutely Elevated Intraocular Pressure?

Hyperosmotic agents, or osmotics, are generally used for short-term intraocular pressure (IOP) control in emergency situations [1] where other medications are unable to lower the IOP [2]. Intravenous (IV) mannitol and oral glycerin (or glycerol) are the most commonly used hyperosmotic agents [1, 3]. Both agents penetrate the blood–ocular barrier poorly, which is a definite advantage, since this fact creates a larger osmotic gradient for water to follow. Other osmotic agents formerly used—isosorbide, alcohol, and urea—have comparable efficacy to mannitol and glycerin but were seldom used because of worse side effect profiles. However, even the currently used osmotics have potentially life-threatening side effects, and they should be used with caution (see Sect. 27.2).

Mannitol can be given either as an IV infusion or IV push. For IV infusion, mannitol may be purchased premixed in 250- or 500-ml bags (Fig. 27.1; mannitol 20%, Hospira Worldwide Inc., Lake Forest, IL; mannitol 20%, B. Braun Medical Inc., Sheffield, United Kingdom; osmitrol 20%, Baxter Medication Delivery, Deerfield, IL). For IV push, mannitol (mannitol 25%, American Regent Inc., Shirley, NY) can be purchased as 50-ml single-dose vials (Fig. 27.2). Because of the limited solubility, storage at room temperature (25°C) is recommended.

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Fig. 27.1 500 ml of 20% mannitol in a plastic bag for intravenous infusion

Mannitol solutions commonly crystallize at low temperatures. If crystallization occurs (Fig. 27.3), the solution should be warmed prior to use. Mannitol should not be administered if crystals are present.

Mannitol is typically administered as an IV infusion using a 20% premixed solution (concentration of 200 mg/mL) at a dose of 1–2 g/kg of body weight [3, 4]. The authors prefer the lower dose of 1 g/kg, which works sufficiently in our experience. Mannitol should be administered intravenously over 30–60 min. Too rapid an infusion of mannitol will cause a shift of intracellular water into the extracellular space, resulting in cellular dehydration with a high risk of hyponatremia, congestive heart failure, and pulmonary edema. Slow administration, over at least 20–30 min, may also avoid transient increases in cerebral blood flow that may exacerbate or increase intracranial bleeding in predisposed patients. Doses in excess of 200 g IV mannitol/day have been associated with acute renal failure.

Although the indications are very rare, mannitol may be administered as an IV push over 3–5 min as a 25% injection. Use of *mannitol IV push* should be reserved for cases where more conservative medical treatments do not lower extremely elevated eye pressures and when an emergent laser or surgical treatment is not possible. The benefits of immediate eye pressure reduction must always be weighed against the significant general medical risks of IV push, and the IV push route is preferably administered by a physician for the reasons noted above. IOP reduction can be seen within 45 min of administration and can last up to 6 h [3]. Peak effect is seen 1–2 h after administration [2].

Glycerin (or glycerol) is usually used as a 50% oral solution at a dose of 1–1.5 g/kg of body weight [3, 5, 6]. Because of its unpleasantly sweet taste, it is often given with juice or over ice [7]. The onset of effect can occur within 10 min, with a peak effect at approximately 1 h [3, 8]. The duration of action is 4–5 h. In elderly

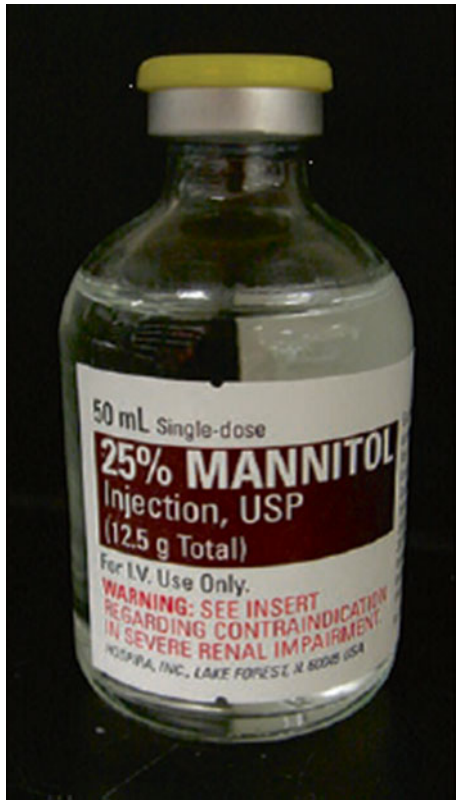

Fig. 27.2 50 ml of 25% mannitol in a single-dose vial for intravenous push

patients, the minimum dose (e.g., 1 g/kg) required to produce the desired effect should be used to avoid serious side effects.

Glycerin was commercially available as Osmoglyn (50% solution, 220-ml bottle by Alcon Laboratories Inc., Fort Worth, TX); however, it is no longer marketed in the United States. We mix our own solution (Fig. 27.4) and use the following recipe for oral glycerin 50% (courtesy of the Massachusetts Eye and Ear Infirmary Department of Pharmacy). The expected yield of this recipe is 900 ml (Table 27.1). The ingredients are Crystal Light™ (a powdered sugar-free drink mix, Kraft Foods, Inc., Northfield, IL), sterile water for irrigation (900 ml), and glycerin USP (450 ml, Humco, Texarkana, TX). The solution can be stored for up to 3 months in a refrigerator. The usual dosage is 2–3 ml of glycerin solution/kg of body weight (approximately 4–6 oz/individual). Glycerin solution can be used in the cardiovascular or severely dehydrated patient with contraindications to mannitol. Isosorbide (Ismotic, no longer marketed in the United States) had been used as an alternative to oral glycerin in patients with diabetes.

The typical dosage and side effects for mannitol and glycerin are summarized in Table 27.2

Fig. 27.3 Two 25% mannitol single-dose vials are shown to demonstrate the absence (*left bottle*) and presence (*right bottle*) of crystals. The higher concentration (25% mannitol) has worse solubility compared with the 20% solution. The crystals can be dissolved by warming and shaking

[1, 5, 6, 9, 10]. Since osmotics are used for the temporary or immediate control of elevated IOP and not for long-term pressure control, the typical dosage of these agents is for one-time use. Repeat administration of osmotics without adequate fluid replacement may lead to a marked state of hyperosmolarity and cellular dehydration, which can result in severe headache, disorientation, and confusion from cerebral dehydration [4]. Although there has been a report of daily administration of oral glycerin for 50 days without evidence of toxicity, long-term therapy and repeat administration of these agents are not recommended [6].

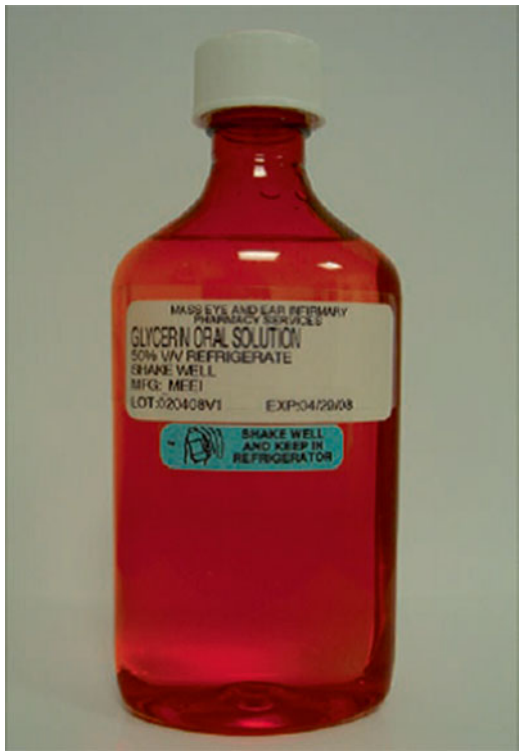

Fig. 27.4 Glycerin oral solution that is prepared according to a recipe from the Massachusetts Eye and Ear Infirmary, Harvard Medical School

Summary for the Clinician

- Mannitol may be given as an IV infusion (20% mannitol) at a dose of 1–2 g/kg of body weight over 30–60 min.
- In truly emergent situations of elevated IOP, an IV push of 25% mannitol injection can be given over 3–5 min by a physician.
- Oral glycerin may be given as a 50% solution at a dose of 1–1.5 g/kg of body weight, with juice or over ice. The usual dosage is 2–3 ml of 50% glycerin/kg of body weight (approximately 4–6 oz/individual).
- Hyperosmotic agents can be used to rapidly lower the IOP for one-time usage, but osmotics are not recommended for long-term use.
- In elderly patients, use the minimum dose required to produce the desired effect.

Table 27.1 Preparation of oral glycerin (glycerol) 50% solution

Ingredients	Procedure	Dosage
Crystal Light (lemon flavored), sterile water for irrigation, glycerin USP	Weigh out 2 g lemon flavored Crystal Light Add the 2 g of Crystal Light to 900 ml of sterile water for irrigation and shake well Measure 450 ml of glycerin q.s. to 900 ml with Crystal Light diluting solution (1:1 ratio of 450 ml glycerin with 450 ml of Crystal Light diluting solution) Stir well to ensure even distribution of components Transfer 225 ml of the solution each to four 240-ml amber plastic bottles, cap, and label Store in a refrigerator (for up to 3 months)	2–3 mL/kg or 4–6 oz/individual

q.s. quantum sufficit (as much as is sufficient, enough)

Table 27.2 Characteristics of mannitol and glycerin (glycerol)

Agent	Metabolism	Dosage (g/kg)	Side effects	Special indications
Mannitol intravenous	Poorly metabolized, passes into urine	1–2 (usually 20% solution or 25% single-dose vial)	Dehydration, chilly sensation, headache, diuresis, dizziness, urinary retention, pulmonary edema, congestive heart failure, intracranial hemorrhage	Vomiting patients, diabetics
Glycerin oral	Metabolic break down in the liver, tubular reabsorption	1–1.5 (50% solution)	Nausea, vomiting, calories, headache	Dehydrated patients, cardiovascular disease

27.2 What Systemic History Should I Gather Prior to Administering Hyperosmotic Agents?

Osmotics are contraindicated in certain systemic conditions, and so past medical history and review of systems must be thorough and include questions regarding cardiovascular status, renal function, diabetes mellitus, and recent water intake.

Because hyperosmotic agents increase the extracellular space, they may precipitate pulmonary edema and cardiac failure in patients with compromised cardiac function [1, 3, 5, 10]. Osmotics should be avoided or used very cautiously in patients with cardiac conditions. These agents are contraindicated in patients with renal failure [1, 3], especially mannitol, as they may induce diuresis and resultant electrolyte imbalance, which may then lead to seizures and coma. In diabetic patients, oral glycerin should be avoided, because it is metabolized to glucose, which can lead to serious hyperglycemia and possibly ketoacidosis. Cellular dehydration, including cerebral dehydration with resultant headache and disorientation, may occur more often with mannitol [3, 10]. Intracranial hemorrhage has also been reported with the use of mannitol [11].

Summary for the Clinician

- Rapid IV infusion of hyperosmotic agents leads to rapid shifts of intracellular water that can lead to hyponatremia, congestive heart failure, and pulmonary edema.
- Hyperosmotics, especially mannitol, are contraindicated in renal failure.
- In patients with compromised cardiac function, the use of hyperosmotics should be restricted.
- Oral glycerin is metabolized to glucose and therefore should be avoided in diabetic patients.
- Intracranial hemorrhage has been reported with IV mannitol.

27.3 Should Hyperosmotic Agents Be Used to Lower IOP Prior to Surgery?

Osmotics have been used to reduce IOP before various types of intraocular surgery [1–3, 5, 7, 12–14]. Only a minority of clinicians advocate the routine use of preoperative hyperosmotic agents. These proponents feel that hypotony and vitreous dehydration are desirable before cataract extraction, corneal transplantation, repair of corneal lacerations, or retinal detachment surgery [5]. A majority of clinicians, however, would consider using osmotics prior to select glaucoma surgeries, especially when the preoperative IOP is very high, i.e., around 50 mmHg. Preoperative lowering of IOP with osmotics is felt to decrease the risk of certain intraoperative and postoperative complications, such as suprachoroidal hemorrhages and decompression retinopathy. These complications are more commonly seen if a very high eye pressure is suddenly dropped to zero at the time of the initial surgical incision [15–17].

When using mannitol infusion preoperatively, 20% mannitol may be given over 60 min starting 1–1.5 h before surgery in order to achieve the maximum IOP reduction before surgery. Although 1 g/kg can be used (Table 27.2), others have suggested using 100 ml of 20% mannitol (20 g dose of mannitol) [2]. The use of mannitol can lower the IOP and increase the anterior chamber depth by dehydrating the vitreous [2, 13]. Six ounces of 50% oral glycerin can be used for the same purpose; however, it may induce problematic vomiting [5]. Since having a patient drink too much fluid prior to eye surgery can create anesthesia concerns, IV mannitol is preferred as a preoperative osmotic. Preoperative ocular digital massage also helps to lower the IOP and reduce positive pressure [13].

Summary for the Clinician

- 20% mannitol may be given intravenously over 60 min, either 1 g/kg or 20 g total, preferably starting 1 h before surgery in order to reduce severe intraoperative/postoperative complications in select predisposed patients.

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References

1. Allingham RR, Damji K, Freedman S, et al. Hyperosmotics. In: Shields' textbook of glaucoma. 5th ed. Lippincott Williams & Wilkins: Philadelphia; 2005.
2. O'Keeffe M, Nabil M. The use of mannitol in intraocular surgery. Ophthalmic Surg. 1983;14:55–6.
3. Singh A. Medical therapy of glaucoma. Ophthalmol Clin North Am. 2005;18:397–408.
4. Hill K. Ocular osmotherapy with mannitol. Am J Ophthalmol. 1964;58:79–83.
5. Feitl ME, Krupin T. Hyperosmotic agents. In: Ritch R, Shields MB, Krupin T, editors. The Glaucomas. 2nd ed. St. Louis: Mosby-Year Book; 1996.
6. McCurdy DK, Schneider B, Scheie HG. Oral glycerol: the mechanism of intraocular hypotension. Am J Ophthalmol. 1966;61:1244–9.
7. Maris Jr PJ, Mandal AK, Netland PA. Medical therapy of pediatric glaucoma and glaucoma in pregnancy. Ophthalmol Clin North Am. 2005;18:461–8.
8. Smith EW, Drance SM. Reduction of human intraocular pressure with intravenous mannitol. Arch Ophthalmol. 1962;68:734–7.
9. Kanski JJ. Carbonic anhydrase inhibitors and osmotic agents in glaucoma. Br J Ophthalmol. 1968;52:642–3.
10. Kolker AE. Hyperosmotic agents in glaucoma. Invest Ophthalmol. 1970;9:418–23.
11. Tsai JC, Forbes M. Hyperosmotic agents used to control acute elevation of intraocular pressure in glaucoma. In: Tsai JC, Forbes M, editors. Medical Management of Glaucoma. 2nd ed. West Islip: Professional Communications; 2004.
12. Awasthi P, Mathur SP, Srivastava MP. Oral glycerol in cataract surgery. Br J Ophthalmol. 1967;51:130–1.
13. Miettinen R, Airaksinen PJ, Pihlajaniemi R, et al. Preoperative timolol and ocular compression in cataract surgery. Acta Ophthalmol (Copenh). 1982;60:622–7.
14. de Ocampo G, Balolong ED, Bernardino Jr V. Preoperative use of mannitol as ocular anti-hypertensive agent. Eye Ear Nose Throat Mon. 1965;44:75–82.
15. Dudley DF, Leen MM, Kinyoun JL, Mills RP. Retinal hemorrhages associated with ocular decompression after glaucoma surgery. Ophthalmic Surg Lasers. 1996;27:147–50.
16. Speaker MG, Guerriero PN, Met JA, et al. A case–control study of risk factors for intraoperative suprachoroidal expulsive hemorrhage. Ophthalmology. 1991;98:202–9.
17. Taylor DM. Expulsive hemorrhage: some observations and comments. Trans Am Ophthalmol Soc. 1974;72:157–69.

Medical Treatment: Neuroprotection

28

Robert N. Weinreb

Core Messages

- Apoptosis is the predominant cause of retinal ganglion cell (RGC) loss in glaucoma.
- Glaucoma neuroprotection enhances the survival and function of RGCs and other neurons within the central visual pathway.
- Neuroprotection is independent of intraocular pressure.
- While there is biological plausibility and experimental evidence for neuroprotection with various drugs, definitive clinical evidence for it still is lacking.

28.1 What Exactly Is Neuroprotection?

Glaucoma is a neurodegenerative disease in which intraocular pressure (IOP) is a leading risk factor [1, 2]. The glaucomatous process is initiated by the acceleration of age-related loss of retinal ganglion cells (RGCs) [2]. Despite IOP lowering, glaucoma still can develop in those at risk and also worsen in those with existing disease [3–6]. Although the risk of glaucoma increases with IOP, loss of RGCs can occur at statistically high, average, or low levels of IOP. While the biomechanics of optic disc cupping—specifically, loss of neuroretinal rim and posterior bowing of the lamina cribrosa—have been extensively studied [7–10], it does not adequately explain why certain patients continue to demonstrate worsening of the disease in spite of apparently low IOP.

In addition to IOP, several other factors are hypothesized to contribute to RGC axonal injury and death including loss of neurotrophic factors, localized ischemia, excitotoxicity, alterations in immunity, and oxidative stress (Fig. 28.1). There is increasing evidence that these factors, triggered by high IOP or occurring independently of IOP, may contribute to pathways with a cascade of events that lead to RGC damage. Neuroprotective therapies seek to ameliorate the impact of these biological factors or pathways on causing RGC damage and then death.

Neuroprotection is a common strategy that has been investigated to treat a variety of neurodegenerative conditions, including ischemic stroke, multiple sclerosis, Parkinson's disease, and Alzheimer's disease. Glaucoma neuroprotection involves the targeted treatment of those neurons

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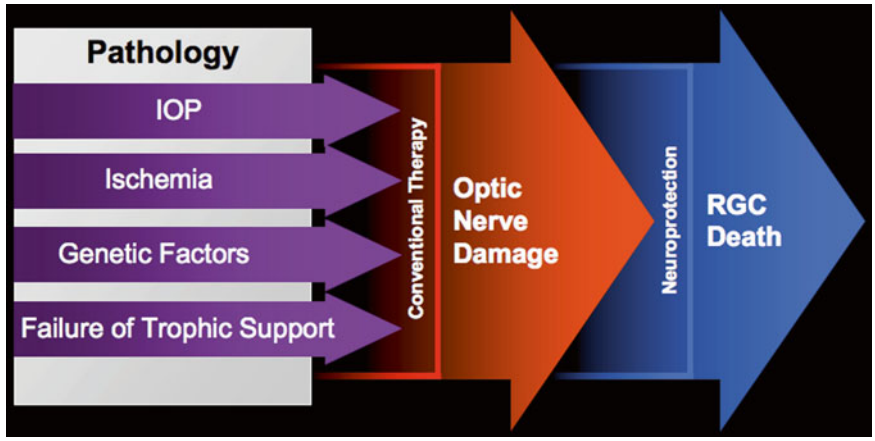

Fig. 28.1 Neuroprotection in glaucoma. Retinal ganglion cell injury may occur by a variety of pathophysiologic mechanisms including increased intraocular pressure, ischemia, genetic factors, oxidative damage, and failure of trophic support. Conventional treatment to prevent optic neuropathy has focused on preventing or mitigating the effect of the inciting factor. Neuroprotection in glaucoma involves targeted modification of the metabolic pathways activated by these inciting factors. *IOP* intraocular pressure (Adapted from Weinreb & Levin. *Arch Ophthalmol* 1999;1(17):1540–4)

that are damaged or likely to be damaged in glaucomatous optic neuropathy, including neurons along the entire visual pathway—but primarily RGC axons. By definition, lowering IOP is not considered to be neuroprotection. Rather, a neuroprotective strategy attempts to stimulate or inhibit specific biochemical pathways that may prevent neuronal injury or stimulate neuronal recovery independent of lowering of IOP. In addition to glaucoma, this strategy may prove meaningful in the treatment of a variety of hereditary or acquired optic neuropathies.

Summary for the Clinician

- Glaucoma neuroprotection targets neurons of the visual pathway for treatment, particularly RGCs that are damaged in the glaucomatous process.
- In neuroprotection, the goal is to directly stimulate pathways that either prevent injury or inhibit specific biochemical pathways that prevent or delay recovery of these neurons.
- By definition, IOP lowering is not considered a neuroprotection strategy even though it can reduce the rate of progressive worsening of glaucoma.

28.2 What Is the Basis of Neuroprotection?

At this time, RGC axons appear to be an initial site of damage in glaucoma. According to the biomechanical model of damage, structural failure of laminar beams and strain along the retinal nerve fiber layer lead to axonal damage. Damaged axons then degenerate via apoptosis (an energy-requiring form of cell death) either in retrograde fashion or by Wallerian degeneration. Axonal transport is disrupted primarily at the level of the lamina cribrosa [11]. A blockade in the axoplasmic flow follows mechanical injury and death of RGCs [11].

The exact pathophysiology of axonal injury and death remains unclear; however, a variety of inter- and intracellular events are triggered during the process of cell death. These events, individually or collectively, are potential targets of neuroprotective strategies (Fig. 28.2). In many neurological diseases, injury can spread to connected neurons by transsynaptic degeneration. The surrounding axons may undergo apoptosis because of the loss of certain neurotrophic factors, such as brain-derived neurotrophic factor and nerve growth factor [12]. In contrast, surrounding axons also may be exposed to upregulated factors that lead to cytotoxicity, such as tumor necrosis

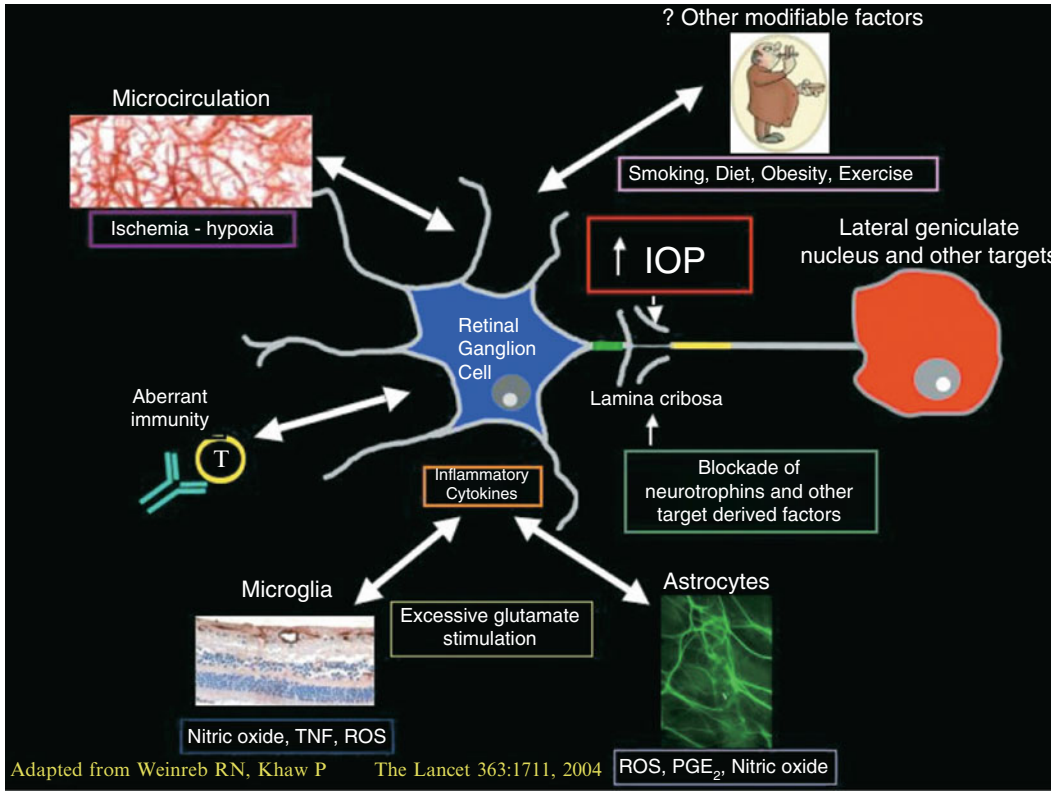

Fig. 28.2 Potential causes of ganglion cell injury. While IOP is the most recognized modifiable risk factor for glaucoma, several other factors, either alone or in concert, may lead to ganglion cell injury and death. Future therapies for patients with optic neuropathies will likely involve recognition and treatment of these idiosyncratic factors. *T* T cell; *TNF* tumor necrosis factor; *ROS* reactive oxygen species; *PGE* prostaglandin E (Adapted from Weinreb and Khaw [2])

factor-α (TNF-α) [13, 14]. It is unclear whether the process of transsynaptic degeneration affects only surrounding RGC axons or whether afferent neurons within the inner retina may also be affected.

Inhibition of intracellular calcium ion (Ca^{2+}) uptake has been a focus of glaucoma neuroprotection because there is an increase in intracellular Ca^{2+} associated with RGC degeneration. Calcium enters cells through voltage-gated channels and *N*-methyl-D-aspartate (NMDA) glutamate receptor-associated channels. An increase in intracellular Ca^{2+} activates calcineurin, which causes the release and activation of apoptotic mediators, such as caspases from mitochondria into the cytoplasmic space [15]. Cytoplasmic Ca^{2+} also stimulates nitric oxide production. The upstream trigger for this cascade of events may be glutamate dependent. Glutamate is a neurotransmitter that binds to the NMDA receptor and promotes Ca^{2+} uptake [16]. An increase in intravitreal glutamate causes RGC death in vitro; however, an increase in intravitreal glutamate has not been observed in experimental models of glaucoma [17]. Glutamate toxicity has also been shown to lead to degeneration of postsynaptic neurons in the lateral geniculate nucleus [18].

Glaucomatous neurodegeneration also appears related to oxidative stress; this leads to mitochondrial fission and mitochondrial dysfunction that generates further oxidative stress, thus perpetuating a vision cycle of RGC injury [19, 20].

Summary for the Clinician

- Potential targets of neuroprotective strategies include
  - Intracellular Ca^{2+},
  - Tumor necrosis factor-α,
  - Nerve growth factors, and
  - Oxidative damage.

28.3 What Medications Are Neuroprotective?

There are several effective neuroprotective therapies that as yet have not been demonstrated to be clinically useful. Why is it so difficult to translate preclinical models of glaucoma to human disease? First, the anatomy of the optic nerve and mechanism(s) of RGC damage (whether IOP is increased or not) in animal models are quite different from those in humans. Next, there are major difficulties in study design between preclinical and clinical glaucoma studies. These include differences in the dose, timing, and duration of intervention. There also are differences in the employed methods and study endpoints. Study animals typically are younger than humans with glaucoma. And, even after being enrolled in a neuroprotection clinical trial humans receive IOP-lowering therapies, whereas studied animals typically are not simultaneously treated with IOP-lowering drugs and a neuroprotective therapy. Finally, experimental models of RGC axonal injury (cell cultures and murine or primate models) do not entirely reproduce the multifactorial pathophysiologic events of glaucoma in humans. Nevertheless, strong experimental evidence for certain medications may lead to their clinical use in the future.

28.3.1 Memantine

Memantine is an NMDA receptor antagonist that blocks the excitotoxic effects of glutamate [16]. The drug has been used to treat Parkinson's and Alzheimer's diseases. Glutamate-mediated synaptic transmission is critical for normal functioning of the nervous system; however, if neurons are injured and unable to properly control the regulation or clearance of glutamate, secondary excitotoxic damage can result. Under pathologic conditions, the NMDA receptor is overactivated and excessive Ca^{2+} influx occurs. Therefore, it was hypothesized that oral memantine theoretically could benefit patients with progressive glaucoma [21]. Memantine has been shown to protect RGCs and brainstem neurons in a monkey model of glaucoma [22]. However, in a Phase III clinical trial, memantine failed to show efficacy compared with placebo when used in patients with glaucoma [23]. Nevertheless, because of the safety profile of memantine and its experimental benefit in preventing axonal injury, patients in whom standard medical or surgical therapy is ineffective or not possible can be offered treatment with memantine with the admonition that it has no proven efficacy in human patients.

28.3.2 Brimonidine

In addition to lowering IOP, alpha-2 adrenergic receptor agonists also increase release of neurotrophic factors, inhibit glutamate toxicity, and reduce Ca^{2+} uptake by neurons in both in vitro and in vivo animal models [24]. This class of medication may also inhibit activation of proteins involved in apoptosis [25]. Alpha-2 receptors are found in a variety of retinal locations and are expressed in RGCs [26]. Brimonidine does protect RGCs from injury in experimental models [27]. Topically administered alpha-2 agonists, such as brimonidine, have been found to achieve neuroprotective intravitreal concentrations [28]. Although there were a number of methodological issues with the Low Tension Glaucoma Study, topical administration of brimonidine better preserved visual field than timolol [29]. Regardless, the neuroprotective effect of brimonidine remains controversial given the medication's accompanying IOP-lowering effect. A clinician also cannot a priori determine whether glaucomatous damage is due

to a pressure-dependent or pressure-independent process. As such, we do not use brimonidine as a first-line treatment for glaucoma when other medications are tolerated that also lower IOP more effectively. Further studies are needed to determine the utility of brimonidine in glaucoma neuroprotection.

28.3.3 Betaxolol

Selective beta-1 adrenergic antagonists (betaxolol) have a similar neuroprotective effect in vitro as the alpha-2 agonists. Betaxolol increases neurotrophin levels, decreases intracellular Ca^{2+}, and blocks glutamate excitotoxicity [30]. However, the concentration required to achieve this effect is non-pharmacologic [31]. Topical administration does not appear to achieve necessary intravitreal neuroprotective concentrations. As such, currently available topical beta-1 adrenergic antagonists should not be used for glaucoma neuroprotection.

28.3.4 Calcium Channel Blockers

Systemic calcium channel blockers (CCB) cause vasodilation by preventing the intracellular uptake of Ca^{2+}. CCBs may improve optic nerve head perfusion [32]. While CCBs have been shown to improve psychophysical testing in a small group of patients, these results have not been confirmed in a large study [33]. Side effects associated with systemic CCBs may limit their practical use. In a prospective population-based study, a positive correlation between systemic CCB use and the development of incident glaucoma was shown [34]. Further prospective studies are needed to determine the safety and efficacy of CCBs. We do not recommend to patients the use of CCBs for treating their glaucoma.

28.3.5 Other Possible Treatments

Several other treatment modalities have shown promising experimental results but have not yet been tested in humans. These include immunomodulation, use of diuretics, TNF-α modulation, selective inhibition of nitric oxide, coenzyme Q [35], and resveratrol [36].

Summary for the Clinician

- Some currently available medications have shown neuroprotective effects in vitro and in animal models; however, results in human clinical trials are either lacking or inconclusive.
- Memantine failed to show efficacy compared with placebo in clinical trials designed to examine whether it slows progression of glaucomatous optic neuropathy.
- Although brimonidine is neuroprotective in experimental models of optic nerve injury, it has not been shown definitively to be neuroprotective in clinical trials.
- Other potential as yet unproven treatments include diuretics, TNF-α modulation, inhibition of nitric oxide, coenzyme Q, and resveratrol.

28.4 Is There a Clinical Role for Systemic Medications in the Treatment of Glaucoma?

The burden of proof for neuroprotective agents is great. Regulatory agencies judge the efficacy of new treatments for glaucoma based on standard white-on-white automated perimetry changes [37]. Progression on standard automated perimetry occurs slowly over many years and can be subtle. A number of clinical studies indicate that standard automated perimetry detects neuronal injury only after considerable damage has already occurred. A sufficiently long-term prospective study with a moderately large population of patients would have to be performed to show efficacy based on current guidelines.

Glaucoma is a multifactorial disease. IOP is clearly a causal factor for axonal injury in patients with both high and low pressures. The subset of patients who progress despite maintaining target IOPs may be good candidates for adjunctive neuroprotective therapy. This includes patients with advanced visual field or central visual acuity loss who are unable to tolerate IOP-lowering medications and are unwilling or unable to have surgery or those who have no alternate form of treatment available.

A clinician must determine which particular treatment will be most effective for an individual patient. Risk factors for glaucoma progression continue to be identified. With such factors (including age, IOP, and central corneal thickness [CCT]), clinicians can individualize their management of each patient and estimate the risk of glaucomatous progression [38].

Summary for the Clinician

- Glaucoma neuroprotection is an IOP-independent method of treating the RGCs that are damaged in glaucoma.
- Currently, there is laboratory evidence indicating that several drugs can prevent experimental RGC injury and death; however, clinical data on human beings are lacking.
- There are no neuroprotective medications for glaucoma approved by regulatory agencies for clinical use at this time.

References

1. Glaucoma Panel. Primary open angle glaucoma preferred practice pattern guidelines. San Francisco: American Academy of Ophthalmology; 2013.
2. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004;363:1711–20.
3. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–11.
4. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6): 701–13; discussion 829–30.
5. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol. 1998;126(4): 487–97.
6. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol. 2000;130(4): 429–40.
7. Yang H, He L, Gardiner SK, Reynaud J, Williams G, Hardin C, Strouthidis NG, Downs JC, Fortune B, Burgoyne CF. Age-related differences in longitudinal structural change by spectral-domain optical coherence tomography in early experimental glaucoma. Invest Ophthalmol Vis Sci. 2014;55(10):6409–20.
8. Gryta R, Sigal IA, Ruberti JW, Meschke G, Downs JC. Lamina cribrosa thickening in early glaucoma predicted by a microstructure motivated growth and remodeling approach. Mech Mater. 2012;44:99–109.
9. Lee EJ, Kim TW, Weinreb RN, Kim H. Reversal of lamina cribrosa displacement after intraocular pressure reduction in open-angle glaucoma. Ophthalmology. 2013;120(3):553–9.
10. Lee EJ, Kim TW, Kim M, et al. Recent structural alteration of the peripheral lamina cribrosa near the location of disc hemorrhage in glaucoma. Invest Ophthalmol Vis Sci. 2014;55(4):2805–15.
11. Quigley HA, Anderson DR. Distribution of axonal transport blockade by acute intraocular pressure elevation in the primate optic nerve head. Invest Ophthalmol Vis Sci. 1977;16(7):640–4.
12. Quigley HA, McKinnon SJ, Zack DJ, et al. Retrograde axonal transport of BDNF in retinal ganglion cells is blocked by acute IOP elevation in rats. Invest Ophthalmol Vis Sci. 2000;41(11):3460–6.
13. Yuan L, Neufeld AH. Tumor necrosis factor-alpha: a potentially neurodestructive cytokine produced by glia in the human glaucomatous optic nerve head. Glia. 2000;32(1):42–50.
14. Tezel G, Wax MB. Increased production of tumor necrosis factor-alpha by glial cells exposed to simulated ischemia or elevated hydrostatic pressure induces apoptosis in cocultured retinal ganglion cells. J Neurosci. 2000;20(23):8693–700.
15. Wang HG, Pathan N, Ethell IM, et al. Ca^{2+}-induced apoptosis through calcineurin dephosphorylation of BAD. Science. 1999;284(5412):339–43.
16. Lipton SA. Paradigm shift in neuroprotection by NMDA receptor blockade: memantine and beyond. Nat Rev Drug Discov. 2006;5(2):160–70.
17. Wamsley S, Gabelt BT, Dahl DB, et al. Vitreous glutamate concentration and axon loss in monkeys with

experimental glaucoma. Arch Ophthalmol. 2005; 123(1):64–70.
18. Gupta N, Yucel YH. Glaucoma as a neurodegenerative disease. Curr Opin Ophthalmol. 2007;18(2): 110–4.
19. Ju WK, Kim KY, Lindsey JD, et al. Intraocular pressure elevation induces mitochondrial fission and triggers OPA1 release in glaucomatous optic nerve. Invest Ophthalmol Vis Sci. 2008;49(11):4903–11.
20. Kim SY, Shim MS, Kim KY, et al. Inhibition of cyclophilin D by cyclosporine A promotes retinal ganglion cell survival by preventing mitochondrial alteration in ischemic injury. Cell Death Dis. 2014;5:e1105 [PMCID: PMC3973219].
21. Lipton SA. The role of glutamate in neurodegenerative diseases including glaucoma. In: Weinreb RN, editor. Glaucoma neuroprotection. The Netherlands: Wolters Kluwer Health; 2006. p. 9–22.
22. Yucel YH, Gupta N, Zhang Q, et al. Memantine protects neurons from shrinkage in the lateral geniculate nucleus in experimental glaucoma. Arch Ophthalmol. 2006;124(2):217–25.
23. Memantine Update. www.glaucoma.org/treating/memantine_updat_1.php. Accessed at 21 Mar 2008.
24. Gao H, Qiao X, Cantor LB, WuDunn D. Up-regulation of brain-derived neurotrophic factor expression by brimonidine in rat retinal ganglion cells. Arch Ophthalmol. 2002;120(6):797–803.
25. Tatton WG, Chalmers-Redman RM, Tatton NA. Apoptosis and anti-apoptosis signalling in glaucomatous retinopathy. Eur J Ophthalmol. 2001;11 Suppl 2:S12–22.
26. Wheeler LA, Woldemussie E, Lai RK. Alpha-2 agonists and neuronal survival in glaucoma. In: Weinreb RN, editor. Glaucoma neuroprotection. The Netherlands: Wolters Kluwer Health; 2005. p. 53–63.
27. Lindsey JD, Duong-Polk KX, Hammond D, Chindasub P, Leung CK, Weinreb RN. Differential protection of injured retinal ganglion cell dendrites by brimonidine. Invest Ophthalmol Vis Sci. 2015;56(3): 1789–804.
28. Kent AR, Nussdorf JD, David R, et al. Vitreous concentration of topically applied brimonidine tartrate 0.2%. Ophthalmology. 2001;108(4):784–7.
29. Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S, Low-Pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-Pressure Glaucoma Treatment Study. Am J Ophthalmol. 2011;141(4):671–81.
30. Zhang J, Wu SM, Gross RL. Effects of beta-adrenergic blockers on glutamate-induced calcium signals in adult mouse retinal ganglion cells. Brain Res. 2003; 959(1):111–9.
31. Hollo G, Whitson JT, Faulkner R, et al. Concentrations of betaxolol in ocular tissues of patients with glaucoma and normal monkeys after 1 month of topical ocular administration. Invest Ophthalmol Vis Sci. 2006;47(1):235–40.
32. Netland PA, Chaturvedi N, Dreyer EB. Calcium channel blockers in the management of low-tension and open-angle glaucoma. Am J Ophthalmol. 1993;115(5): 608–13.
33. Boehm AG, Breidenbach KA, Pillunat LE, et al. Visual function and perfusion of the optic nerve head after application of centrally acting calcium-channel blockers. Graefes Arch Clin Exp Ophthalmol. 2003;241(1):34–8.
34. Muskens RP, de Voogd S, Wolfs RC, et al. Systemic antihypertensive medication and incident open-angle glaucoma. Ophthalmology. 2007;114(12):2221–6.
35. Lee D, Shim MS, Kim KY, et al. Coenzyme Q10 inhibits glutamate excitotoxicity and oxidative stress-mediated mitochondrial alteration in a mouse model of glaucoma. Invest Ophthalmol Vis Sci. 2014;55(2): 993–1005.
36. Lindsey JD, Duong-Polk KX, Hammond D, et al. Protection of injured retinal ganglion cell dendrites and unfolded protein response resolution after long-term dietary resveratrol. Neurobiol Aging. 2015;36(5): 1969–81.
37. Weinreb RN. Glaucoma neuroprotection: what is it? Why is it needed? Can J Ophthalmol. 2007;42(3): 396–8.
38. Medeiros FA, Weinreb RN, Sample PA, et al. Validation of a predictive model to estimate the risk of conversion from ocular hypertension to glaucoma. Arch Ophthalmol. 2005;123(10):1351–60.

29 Medical Treatment: Treated vs. Untreated Glaucoma and Ocular Hypertension

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Core Messages

- The study design most amenable to assessing the natural history of a chronic disease like glaucoma is a prospective observational cohort study; however, these studies are rare.
- Understanding the natural history of untreated and treated glaucoma is limited by the inability to directly compare glaucoma progression in treated vs. untreated eyes over the entire range of glaucoma severity.
- Multiple studies have proven the benefit of lowering intraocular pressure (IOP) in decreasing the conversion rate of ocular hypertension to glaucoma and lowering the progression rates of already existing glaucoma.
- Glaucomatous optic neuropathy may progress despite aggressive lowering of IOP, suggesting a multifactorial cause of this chronic disease.
- Glaucoma treatment should focus on each patient as an individual while using results from long-term trials and retrospective reviews to help guide the need for and level of aggressiveness for therapeutic interventions.

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29.1 What Is the Natural History of Treated and Untreated Glaucoma and Ocular Hypertension?

Understanding the natural history of chronic disease is difficult, and for ethical reasons it is particularly difficult to study the natural history of an untreated disease for which beneficial treatment is available. The study design that is most amenable to assessing the natural history of a chronic disease is an observational cohort study. However, because of the large number of subjects and long time duration needed to obtain the answer of interest, conducting these studies may not be feasible. Data from other study designs are typically used to infer the natural history of chronic diseases. Such is the case with open angle glaucoma (OAG).

Though many barriers exist to planning and conducting a prospective observational study to follow the natural history of a disease, occasionally an opportunity presents itself to "observe" a

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cohort retrospectively. One such cohort of glaucoma patients was retrospectively followed in Olmsted County over 16 years [1]. These patients received routine care, predominantly in a university setting, and were treated with available treatments of the era. Another cohort of glaucoma suspects and subjects in St. Lucia was examined 10 years after initial diagnosis [2, 3]. These subjects were not treated during this 10-year time span due to a variety of reasons including a lack of resources. There are major methodological limitations in both of these studies that warrant caution when interpreting the findings.

A unique aspect of the St. Lucia study was that it offered an opportunity to observe outcomes in untreated glaucomas. Except in very limited circumstances, it would be unethical to design a prospective study of untreated glaucomatous eyes. The Collaborative Normal Tension Glaucoma Study (CNTGS) and the Early Manifest Glaucoma Treatment Trial (EMGT) are both clinical trials that included an untreated cohort [4–6]. Although clinical trials are not optimal for studying the natural history of a chronic disease, information derived from EMGT and CNTGS supplement the information derived from the observational studies noted above (Olmsted County and St. Lucia) to provide a better understanding of the natural history of treated and untreated OAG.

The situation with ocular hypertension differs from that of OAG in that it is not considered a disease, but rather a risk factor for the disease. Additionally, because numerous studies to assess the benefit of treating ocular hypertension had yielded inclusive results, there existed no ethical barriers to designing a long-term clinical trial of untreated vs. treated patients with elevated intraocular pressure (IOP). With the completion of the Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS), the natural history of untreated vs. treated ocular hypertension is now well established [7–9].

We will summarize the design and findings of these studies and explain how each contributes to our knowledge of the natural history of OAG and of ocular hypertension.

29.2 What Is the Natural History of Treated and Untreated Glaucoma?

29.2.1 Olmsted County, MN

In a retrospective community-based incidence study, the Rochester Epidemiology Project database was used to access information on the 60,666 residents of Olmsted County, MN [1]. During the 16-year study interval, 114 patients were newly diagnosed with OAG. Eighty-nine percent (102/114) of patients with OAG had POAG. Annual incidence was noted to increase with age, ranging from 1.6/100,000 in the fourth decade of life to 94.3/100,000 in the eighth decade. While incidence rates peaked during the eighth decade, there was a notable decrease in incidence rates in the ninth and tenth decade of life. This downturn was attributed to either the small number of patients in this age group or alternatively to the tendency of physicians not to treat existing POAG in these upper decades of life.

The overall gender and age-adjusted annual incidence rate was about 14.5 per 100,000, and gender was not noted to have a significant effect on incidence. Also of interest was the change in annual incidence rate of OAG in the last 2 years of the study (27.2 per 100,000) compared to earlier in the study (12.3 per 100,000). The authors suggested that this difference was due to the introduction of timolol in October of 1978. The existence of a relatively well tolerated and effective therapy may have made physicians more likely to diagnose OAG. Alternatively, the presence of a new therapy may have exposed physicians to new education about OAG and made them more likely to diagnose the disease.

In a 1998 report examining the Olmsted County retrospective data set, the probability of unilateral blindness was reported to be 27 % and bilateral blindness was 9 % after 20 years in the 295 patients classified as having classic glaucoma and ocular hypertension [10]. Blindness was defined as visual field constriction to within 20° of fixation or visual acuity of 20/200 or worse.

In the "classic" glaucoma subgroup analysis, there was a 22 % probability of bilateral blindness and 54 % probability of unilateral blindness at 20 years. (Classic glaucoma was defined as meeting two of three of the following: IOP ≥ 21 mmHg, optic nerve damage, and/or visual field defects. Of note, 89 % of patients had IOP ≥ 21 mmHg.) In the treated ocular hypertension group, cumulative probability for bilateral and unilateral blindness was 4 % and 14 %, respectively. It must be noted that during most of the time of this retrospective review, timolol and laser trabeculoplasty were not available treatment options.

The Olmsted County retrospective review clearly documented that the incidence of glaucoma increased with advancing age. The study is limited by its retrospective design, which did not allow for standardized treatments and data collection. Also, attempting to use data from this study to better understand the natural history of treated POAG today is limited due to the use of an entirely different group of medications. Beta blockers were not available for most of the study period, and selective alpha-agonists and prostaglandin analogs were years away from the marketplace. It could be argued that in comparison to currently available medications, these patients were sub-optimally treated and may be more aptly classified as not treated. Another limitation of the data is that the population was almost exclusively Caucasian (98 %) with considerable Scandinavian ancestry. The information obtained, while instructive, cannot probably be generalized to other racial/ethnic groups.

29.2.2 St. Lucia Study

The initial St. Lucia Eye Study was conducted in 1986/1987 and documented the prevalence of POAG on the Caribbean island country [2]. This population-based survey included 1679 subjects; 364 glaucoma subjects and glaucoma suspects were identified. Ten years later, a repeat examination was executed of the cohort of glaucoma subjects and glaucoma suspects who were still living and residing in St. Lucia, who had not undergone glaucoma surgery, and who were not being medically treated ($n = 205$) [3].

Humphrey 30-2 threshold visual fields were obtained at both the initial 1987 survey and the 1997 follow-up examination. Both sets of visual fields were converted to a format suitable for grading by criteria established and used by the Advanced Glaucoma Intervention Study (AGIS) and the Collaborative Initial Glaucoma Treatment Study (CIGTS). Studies comparing these two grading algorithms have found the AGIS algorithm to yield more conservative results than the CIGTS algorithm.

Using the AGIS criteria, 80 of 146 right eyes and 73 of 141 left eyes had progressed. Of the eyes that had progressed, 24 of the 80 right eyes (30 %) and 21 of the 73 left eyes (29 %) had progressed to end-stage glaucoma. Overall, the probability of reaching an "end-stage" visual field end point in at least one eye was 16 % at 10 years.

The study population was exclusively black, and thus, generalizations from this study are limited. The best comparison of visual field progression in treated vs. untreated glaucomatous eyes is made by comparing the results of this study with a study that used the same definition of progression. Although the comparison is not ideal, the AGIS had subjects with varying levels of glaucoma severity, all the subjects were treated, the same visual field scoring algorithm was used, and the data allows comparison with black subjects only. Extrapolating from the percentage of black subjects with visual field loss progression at 7 years in AGIS (30 %), the percentage of black AGIS subjects with visual field progression at 10 years would be approximately 43 % (assuming that the percentage increases linearly). In the St. Lucia follow-up study, a considerably larger percentage of untreated eyes progressed—53 %. Keep in mind that the AGIS and St. Lucia patients may not be equal in terms of baseline visual field loss.

29.2.3 Collaborative Normal Tension Glaucoma Study

The CNTGS was designed to measure the efficacy of a 30 % IOP reduction on the rate of glaucoma progression in patients with pressures

considered to be in the normal range (i.e., low or normal tension glaucoma) [4]. Eligible eyes had to manifest glaucomatous optic nerve excavation and a field defect consisting of a cluster of three non-edge points depressed by 5 dB, with one of the points also depressed by 10 dB (two of three baseline tests over 4 weeks had to agree). Progression was suspected if: (1) at least two contiguous points within or adjacent to a baseline defect showed a reduction in sensitivity from baseline of ≥10 dB or if the reduction noted was three times the average baseline short-term fluctuation for that subject, (2) the sensitivity of each suspected point was outside the range of values observed during baseline testing, or (3) a defect occurred in a previously normal part of the field. Classification of a patient as "progressing" required agreement on four tests.

One hundred and forty eyes of 140 patients were used in this study (61 treatment and 79 control). Twenty-eight (35 %) of the control eyes and 7 (12 %) of the treated eyes reached either visual field or optic nerve end points for progression. The mean time to progression was 2688 ± 123 and 1695 ± 143 days for the treated and control groups, respectively ($p < 0.0001$). The authors concluded that IOP is part of the pathogenic process in normal tension glaucoma. A follow-up report in 2001 focused specifically on 160 CNTGS patients who were untreated among a total enrollment of 260 [11]. Of these 160 patients, 49 were randomly assigned on enrollment to not receive therapy, 24 were followed without treatment until later being randomly assigned to treatment (due to progression by visual field testing or optic nerve examination), 31 were followed without treatment and were later randomly assigned to be followed for additional time without treatment, and 56 were enrolled but were never randomly assigned. Outcome measures focused only on those visual fields obtained during the time in which the eye was not under treatment. Progression was noted as the "survival" time to meeting a criterion of localized progression and rate of change in the mean deviation (MD) over time. Approximately one-third of all patients showed localized progression within 3 years and about half showed progression within 5–7 years using Kaplan–Meier analysis. Sixty-two of 109 patients followed for 3 years or more did not show a statistically significant negative slope of MD regressed over time.

One of the most important lessons from the CNTGS is the fact that the rate of progression without treatment is highly variable from patient to patient and often so slow that half of the patients have no progression after 5 years. Risk factors for quicker progression included female gender, history of migraine headaches, and the presence of disc hemorrhages.

This study is limited in its ability to tell us about the natural history of glaucoma since eyes were excluded once they reached a clearly defined end point (progression on visual field). Another limitation is its lack of generalizability. In CNTGS a specific subset of OAG patients who have normal or low IOP were studied. Although perhaps a minority opinion, some ophthalmologists believe that so-called normal tension glaucoma is fundamentally different from primary OAG. Whether this sentiment is true or not, the appropriateness of generalizing findings from this subset of glaucoma patients to the broader community of glaucoma patients is debatable.

29.2.4 Early Manifest Glaucoma Treatment Study

The EMGT, a large, controlled clinical trial, randomized patients ($n = 255$) with early OAG either to IOP lowering therapy or observation [5, 6, 12]. The treated group was assigned to Betaxolol and argon laser trabeculoplasty, and it received Xalatan whenever IOP exceeded 25 mmHg at more than one visit. As a safety precaution, patients in the observation group whose IOP rose to 35 mmHg or higher also received Xalatan therapy. After this sequence, patients whose IOPs were deemed too high were then treated according to the standards of the treating physician.

Progression was defined perimetrically using Humphrey 30-2 "pattern deviation change probability maps" and by determination of optic disc progression using photography and flicker

chronoscopy. After a mean follow-up period of 6 years, progression was noted in 78 of 126 (62 %) patients in the observation group and in 58 of 129 (45 %) patients in the treatment group. Determination of progression was based on visual field change in all patients with the exception of one subject in which it was based on optic nerve change.

Because of the ethical considerations inherent in withholding treatment for eyes that would likely benefit from treatment, the study population was highly selective and a number of safety interventions that precluded the long-term observation of many untreated patients were allowed. Also, as with the CNTGS, long-term observation was further limited by the exclusion of patients once they reached a clearly defined progression end point.

Summary for the Clinician

- There are major limitations to understanding the natural history of untreated vs. treated glaucoma, specifically, the inability to directly study and compare glaucoma progression in treated vs. untreated eyes over the entire range of glaucoma severity.
- Clinical generalizations made from available studies are limited due to narrow designs that make assumptions specific only to the study populations.
- Both the Olmsted County and St. Lucia Studies have limitations noted above but are observational studies that document substantial progression from suboptimal (Olmsted) and no treatment (St. Lucia).
- Both the CNTGS and EMGT are randomized clinical trials that included a group that received no treatment. They helped to establish the beneficial effect of treatment vs. no treatment on glaucoma progression.

29.3 What Is the Natural History of Untreated vs. Treated Ocular Hypertension?

29.3.1 Ocular Hypertension Treatment Study

Until recently, no consensus existed as to whether eyes with elevated IOPs should be medically treated or not. Multiple studies examining this question were either inconclusive or yielded contradictory results. The OHTS was designed to definitively answer this question. Begun in 1994, the initial results of this large-scale, multicenter clinical trial were published in 2002 [7]. The study population included 1636 people 40–80 years of age who had elevated eye pressure (24–32 mmHg) but showed no signs of glaucoma by either visual field or optic nerve head exam. Half of the patients were assigned to daily topical glaucoma drops and the other half was assigned to observation. All enrollees had sequential visual field examination and optic nerve head photography. IOP lowering was 22.4 % in the treatment arm and stable in the control arm (–4.0 %).

Baseline factors that were predictive of developing glaucomatous optic neuropathy included older age, higher IOP, lower central corneal thickness (CCT), larger vertical cup-to-disc ratio, and higher pattern standard deviation. Overall, 4.4 % of the treatment group advanced to POAG while 9.5 % of the observation group progressed by visual field and/or optic nerve changes. This translates to a number-needed-to-be-treated (NNT) of 16 patients to prevent one case of glaucoma in 5 years.

29.3.2 The European Glaucoma Prevention Study

As with OHTS, the EGPS was a randomized, multicenter, controlled trial designed to evaluate the efficacy of IOP reduction in preventing or delaying the development of OAG in ocular hypertension subjects [8, 9]. The entry criteria for patient enrollment were substantially similar to

that for OHTS and 1081 patients were enrolled. However, unlike in OHTS, subjects randomized to treatment received dorzolamide only. Dorzolamide reduced IOP in treated patients by a mean of 15 % after 6 months and 22 % after 5 years. The NNT with dorzolamide to prevent one case of glaucoma was 143 patients. Interestingly, IOP also declined in the observation group by a mean of 9 % and 19 % after 6 months and 5 years, respectively. As might be expected with similar IOP reductions between groups, the cumulative probability of developing an end point after 5 years of follow-up was not significantly different statistically between the two randomized groups. However, the EGPS did find that higher mean IOP at baseline in both treated and untreated subjects was significantly associated with the development of glaucoma. Thus, as with OHTS, the significance of IOP in the pathogenesis of glaucoma was affirmed. Perhaps the most important contribution of EGPS was that the predictive factors for glaucoma development found in OHTS were validated in an independent study population.

Summary for the Clinician

- The OHTS and EGPS clearly show that high IOP is a risk factor for developing glaucomatous optic neuropathy and that lowering IOP decreases the conversion rate from ocular hypertension to manifest glaucomatous optic neuropathy.
- EGPS limited treatment of patients to topical dorzolamide, thus not mimicking the initial treatment choice of prostaglandin analogs used in most practices today. It is unclear how this influenced findings in this study.
- The number-needed-to-treat (NNT) in OHTS is 16 ocular hypertensives to prevent one case of conversion to glaucoma using a 20 % IOP reduction.
- The NNT in EGPS is 143 ocular hypertensives to prevent one case of conversion to glaucoma using dorzolamide alone.

References

1. Schoff EO, Hattenhauer MG, Ing HH, et al. Estimated incidence of open-angle glaucoma in Olmsted County, Minnesota. Ophthalmology. 2001;108(5):882–6.
2. Mason RP, Kosoko O, Wilson MR, et al. National survey of the prevalence and risk factors of glaucoma in St. Lucia, West Indies. Part I. Prevalence findings. Ophthalmology. 1989;96(9):1363–8.
3. Wilson MR, Kosoko O, Cowan Jr CL, Crandall D, et al. Progression of visual field loss in untreated glaucoma patients and glaucoma suspects in St. Lucia, West Indies. Am J Ophthalmol. 2002;134(3):399–405.
4. Collaborative Normal Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol. 1998;126: 487–97.
5. Leske MC, Heijl A, Hyman L, et al. Early manifest glaucoma trial: design and baseline data. Ophthalmology. 1999;106:2144–53.
6. Heijl A, Leske MC, Bengtsson B, Early Manifest Glaucoma Trial Group, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Arch Ophthalmol. 2002;120:1268–79.
7. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6): 701–13; discussion 829–30.
8. Miglior S, Zeyen T, Pfeiffer N, European Glaucoma Prevention Study (EGPS) Group, et al. Results of the European Glaucoma Prevention Study. Ophthalmology. 2002;112(3):366–75.
9. Miglior S, Pfeiffer N, Torri V, European Glaucoma Prevention Study (EGPS) Group, et al. Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. Ophthalmology. 2007; 114(1):3–9.
10. Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. Ophthalmology. 1998;105(11):2099–104.
11. Anderson DR, Drance SM, Schulzer M, Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal-tension glaucoma. Ophthalmology. 2001;108(2):247–53.
12. Leske MC, Heijl A, Hussein M, Early Manifest Glaucoma Trial Group, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121(1): 48–56.

Medical Treatment: Adherence and Persistence

30

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Core Messages

- Adherence to eye drops and persistence of medication is a significant problem among the glaucoma population.
- Physicians cannot accurately identify patients who are nonadherent.
- An open and nonjudgmental discussion with patients is critical.
- Overcoming obstacles like nonadherence requires education, reassurance, and support from the eye care team.

30.1 What Issues Are at Work in Patient Noncompliance?

Glaucoma is recognized as a significant cause of blindness worldwide. It is a disease that affects over two million people in the United States today, a number that is projected to increase to more than three million by the year 2020. The mainstay of therapy for open-angle glaucoma is maintaining low intraocular pressure to prevent or retard progression of the disease. However, despite the possibility of devastating vision loss, low adherence to and persistence on medical treatment remains surprisingly poor. Unfortunately, glaucoma is one of the many chronic diseases in which poor adherence leads to disease progression, which in turn leads to increased health costs. In fact, hospital admission data in the United States show that 33–69 % of all admissions are the result of noncompliance with medications, costing the system approximately $100 billion a year [1, 9, 10, 16]. Understanding the motivating or demotivating factors behind these behaviors is essential to provide quality care to our patients. The two key concepts involved are those of *adherence* and *persistence*.

30.1.1 What Is Adherence?

Adherence is defined as the regular use and correct administration of medication as prescribed by healthcare professionals. This is preferred over the term "compliance" which has the disadvantage of conveying a passive role for the patients, a role in which the patients follow orders. Adherence denotes an active participatory role based on a common therapeutic goal for both the practitioner and patient. Interestingly, adherence is usually highest in 5 days preceding the appointment, a phenomenon known as "white-coat adherence" [12]. Obviously, this phenomenon can confound treatment objectives and account for progression at seemingly controlled pressures.

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30.1.2 What Is Persistence?

Persistence describes the period of time when there is consistent use of the prescribed medical regimen. With regard to persistence with glaucoma medications, clinical studies demonstrate that most patients discontinue their medical therapy within the first 6 months of treatment [5, 11, 14, 15]. Friedman et al. used pharmacy claims data to study compliance and found that only 10 % of patients had continuously refilled their medication during the first year of therapy [3]. Clearly, a determination of the issues involved is necessary to prevent perpetuation of this behavior and eventual loss of vision in the glaucoma population. Adherence and persistence rates vary with estimates at 3 years after initiation of treatment ranging from 15 to 58 % [16].

30.1.3 What Are the Challenges Facing Patients in Terms of Adherence and Persistence?

There are a variety of challenges that patients face with adherence to a medical regimen. Lack of motivation is the main adversary, especially when dealing with the concept of lifelong therapy of an asymptomatic disease. It is often difficult to accept the diagnosis in the first place and then to acquiesce to the daily intrusiveness of eye drops, which may have irritating side effects. At the time of diagnosis, it is helpful to educate the patient about the disease. Having the patient watch informational videos with their family members and then giving them literature to take home may dispel fears about their diagnosis. Only after they have digested the significance of having glaucoma, treatment principles can be reviewed and discussed thoroughly. Before that, their fears may impair their ability to process new information. Taking the time to give patients full disclosure of the common side effects encountered with their new medications is invaluable to ensuring persistence. Also, patients need to be reminded and educated about the importance of maintaining lowered intraocular pressure during every subsequent visit. Repetitive inquiry about medication use is essential to confirm persistence to the treatment regimen. Open communication can only further engender a trusting patient–physician relationship.

It is critical not to neglect the fact that social and cultural issues play a role in poor adherence among groups of different ethnicities. A study by Owsley et al. interviewed focus groups of older African Americans and their eye physicians [13]. They found that among older African Americans, trust and open communication were significant barriers to adherence. In contrast, the eye care providers interviewed did not perceive that communication was a problem with their patients. This suggests that eye physicians must be aware of different communication needs that different patients have. Social and cultural factors may be impediments to adherence as a reflection of inadequate access to healthcare, deficient income, and distance to providers. It is important to identify these limiting factors so that arrangements can be made to prevent gaps in treatment. Furthermore, incorporating a reminder system for appointment scheduling and follow-up for missed appointments is important [8, 17, 18].

Other reasons behind poor adherence include the demographics and lifestyle interests of the glaucoma population. Most patients are elderly with numerous comorbidities that may increase their medication and cost burden. Apart from problems with instilling medications, another major obstacle is remembering to use them. Patel and Spaeth ascertained that the main reasons patients do not follow a medication schedule include forgetfulness (39 %), being away from home and medications (26 %), inconvenient timing and frequency (9 %), and side effects (2 %) [14]. From this study, we can ascertain that incorporating new medications into any patient's daily routine creates formidable obstacles.

Summary for the Clinician

- Despite the real possibility of vision loss, adherence and persistence to medical treatment is surprisingly low—estimated to be 15–58 % 3 years after initiation of therapy.

- Adherence is the regular use and correct administration of medications as prescribed.
- Persistence is the period of time in which there is consistent use of the prescribed regimen.
- The asymptomatic and chronically progressive nature of glaucoma contributes to the problems of adherence and persistence.
- Acceptance of the diagnosis, intrusiveness of treatment, lack of education, fear, and social/cultural issues in different ethnicities also contribute to the problem.

30.2 How Can One Help Patients to Be More Compliant with Treatment?

The key to promoting adherence is participating in active and open discussions with our patients regarding their medication usage. It is a well-established fact that physicians cannot predict which patient will be adherent, and therefore the onus is on us to help encourage medication use through nonjudgmental dialogue [7, 18]. Phrasing questions empathetically such as, "Sometimes it is hard to add a new medication into your daily routine. Have you been able to do this successfully?" Acknowledging that missing doses is a common problem sets an accepting tone that promotes frank disclosure of medication usage or nonuse. Patients are usually not forthcoming with admissions of poor adherence, as they would rather fulfill the role of the "good" patient. Self-reported compliance may be highly overrated as demonstrated by Kass et al. who monitored patient compliance with an electronic device and found that patients self-reported a substantially higher rate of adherence than what was measured by the monitor [7]. As a physician faced with possible medication failure to control IOP, it is even more critical to actively discuss medication use with the patient.

To encourage a helpful discussion regarding medication usage, it is salient to remember to ask directed questions. When asking if a patient has taken his/her eye drops, phrase it as an open-ended question and not as one that will elicit a simple yes or no answer. One example would be to ask the patient to tell you how they use their medication, therefore requiring an explanatory answer. During the office visit, try to ascertain reasons why drops are not being used. Patients may have issues with comprehension of the disease, why they have to take drops, ability to instill medications, or lack of a support system. Although the time with our patients may be limited by our burgeoning clinic schedules, it is important to decipher and address them early on. Also, never underestimate the ability of members of your eye care team. The technicians can easily identify these issues while working up the patient and therefore provide the physician with invaluable information.

However, identifying patients is only half the battle. The other half is discovering a means to overcome the patient's difficulties. Tsai et al. identified and categorized barriers that create noncompliance as seen in Table 30.1 [19]. Certainly, some of these factors are beyond control, but working with our glaucoma population to overcome some of the stated obstacles in Table 30.1 can certainly supply essential tools for adherence. For instance, having family members present during visits provides a second set of ears that can remind the patient of important instructions. Involving family members and friends automatically recruits them as a ready support system for the patient.

With the ever-changing landscape of medical insurance, patients face a quagmire of difficult decisions about medical plans. For those who cannot afford glaucoma medications, many pharmaceutical companies offer special assistance programs. Offering to help set up patients in these programs can only further solidify their trust in your care. Also, accommodating changes in drug coverage requires awareness and plasticity on the physician's part to readily substitute medications and fill the needs of the patient.

Table 30.1 Barriers to adherence and persistence

Situational/environmental factors (49 %)
Lack of support
Major life events
Travel away from home
Competing activities
Change in routine
Medication regimen factors (32 %)
Refills
Cost of medications
Complexity
Side effects
Patient factors (16 %)
Knowledge
Memory
Motivation
Comorbidities
Provider factors (3 %)
Dissatisfaction
Communication

Summary for the Clinician

- Participate in active and nonjudgmental discussions with patients regarding medication usage.
- Use directed, open-ended, empathetic questions.
- Be aware that the patient may be trying to please you, the physician, with their answers.
- Try to ascertain why drops are not being used as directed. Your eye care team can be helpful with this ascertainment.
- Table 30.1 categorizes reasons barriers to nonadherence.
- Recruit family members to visits as a second pair of ears and a support system for the patient.
- Insurance can create barriers as well. Be knowledgeable about special assistance programs the patient can take advantage of and be flexible about changes in drug coverage.

30.3 How Can One Educate Patients to Realize the Long-Term Impact of Glaucoma and Encourage Adherence?

Approaching adherence to glaucoma treatment mirrors the chronicity of the disease; it is an ongoing pursuit. Every follow-up visit is a chance to underscore the importance of daily administration of medications. Building a solid physician–patient relationship with clear communication reinforces a patient's faith in benefit of treatment and therefore their likelihood to follow up with care [2, 4]. As stated earlier, knowledge and comprehension of glaucoma empowers the patient to take an active role in their eye care. Handing out educational brochures helps to solidify their understanding. If patients are continuously confused about when to take their medications, provide them with a dated medication schedule that clearly outlines in which eye the medication is to be used, how many times a day, and how many hours apart (Table 30.2). Associating the color of the cap of the bottle with the medication name considerably facilitates medication identification. This is especially important in patients with multiple eye drops. Also, remind them that the drops need to be separated by at least 5 min when there are different drops at the same dosing time.

First time drop users should be identified and instructed by your staff about proper techniques of eye drop administration. Usually, informational videos about glaucoma cover this area but it never ceases to amaze us how many people who present for follow-up care already taking drops still comment that they were never really taught how to instill them. In our office, we compile a list of first time drop users and follow-up with a call later in the month to check in with the patient and answer any further questions they might have. Often at the time of instruction, we have the patient demonstrate drop instillation with a bottle of artificial tears so that we can critique technique and make helpful suggestions. Also at the time of initiation of medical therapy, encourage the patient to link drop usage with a habitual daily activity. For instance, the patient may choose to store the eye medications in the bathroom so that he or she can link the administration of eye drops to dental hygiene. Counseling the patient on potential side

Table 30.2 One example of a chart that can be handed out to patients to help minimize confusion regarding drop instillation

Drop(s) to use	Right eye	Left eye
Lumigan	One drop daily at night	One drop daily at night
Travatan		
Xalatan		
Timolol	One drop once daily in the morning	One drop once daily in the morning
	One drop two times daily	One drop two times daily
Alphagan	One drop two times daily	One drop two times daily
Brimonidine	One drop two times daily	One drop two times daily
Azopt	One drop two times daily	One drop two times daily
Trusopt	One drop three times daily	One drop three times daily
Cosopt	One drop two times daily	One drop two times daily
Combigan	One drop two times daily	One drop two times daily

Brand name or generic name is circled or highlighted. Also circle or highlight frequency of instillation in the correct column corresponding to the eye that should receive the drop
Twice daily drops should be used in the morning and evening. Three times daily drops should be used morning, afternoon, and evening. Allow 5 min between drops. Close your eyes or press along the inner corners of your eyes after instilling drops

Table 30.3 American Glaucoma Society's Patient Care Project ideas to augment patient compliance

- Glaucoma buddy system so patients can remind each other of appointments
- Expose patients to the experience of others who may have lost functional vision to glaucoma
- While in the office, have patients write themselves a note about their next appointment. Office staff mails the note 10 days before their next appointment
- Inquire of patients how they are coming to their visits and help with any potential transportation difficulties
- Provide educational materials about
  - Glaucoma medications and their possible side effects
  - Why follow-up is needed
- At each visit, ask patients what they would like to know about their eyes
- Have patients add alerts about upcoming appointments to their PDA devices
- Have pharmacists alert doctors' offices when a patient has not refilled medications for 1–2 months
- Provide patients with colored handouts that show pictures of the medication. Include a drop schedule, easy to follow chart, or laminated daily dosing chart with medication names and time of day to take. Provide patient with a dry erase marker to cross out time after instillation
- Lobby for unit-dose glaucoma medications. Having Monday through Sunday packs would clearly indentify missed medications
- Design a tilted eye drop bottle with the dropper part on an angle to the well of drops to make it easier to get the bottle at the proper angle to the eye

effects is very important to ensure adherence and persistence. Reminding patients to either keep their eyes closed for a minute or practice punctual occlusion as a means to decrease drug absorption into the nasal mucosa also decreases likelihood of these side effects.

The importance of simplifying a medical regime cannot be overstated. Stewart et al. found that once a day dosing increased patient satisfaction [18]. Adherence is highest among the patients taking the prostaglandin analogs [11]. This is hardly a surprise as these agents are highly effective, have the least worrisome side effects, and most importantly, require only one daily dosage. However, most patients require more than one medication as demonstrated by the Ocular Hypertension Treatment Study, which found that at 5 years, 40 % of subjects required more than one medication to achieve the target pressure of 20 % below baseline [6]. When adjunctive therapy is needed, adding a second medication that also requires a once-daily regime, such as a beta-blocker agent dosed in the morning, maintains an uncomplicated regimen. Formulas combining two different drugs into a single drop can be helpful in further simplifying dosing. Importantly, always keep in mind the potential cost of new medications so that affordability doesn't become a major problem for adherence.

Local support groups also offer additional assistance for our patients. These groups can provide a forum for discussion and interchange of ideas that transfer essential tools to understand and cope with glaucoma. Have this information readily available to the patients as a handout or posted on a bulletin board in the waiting room.

The American Glaucoma Society's Patient Care Project was undertaken to award ideas that could augment patient compliance. The best ones are listed in Table 30.3. In addition, it is helpful to identify those with low or limited vision in order to address their special needs and to provide them with information about local low vision clinics.

In conclusion, adherence is a major problem that we all have to contend with when treating a patient with glaucoma. It is not easy to identify patients who have trouble with their medication usage, and it is therefore essential to approach each glaucoma patient in a consistent manner, one that underscores education, empathy, and active dialogue. With these tools we can surely overcome barriers to adherence and create a strong patient–physician relationship.

Summary for the Clinician

- Every follow-up visit with a glaucoma patient is a chance to underscore the importance of regular use of prescribed medications.
- Education empowers the patient. Educational brochures and videos are useful. Have your office staff instruct patients on how to instill drops and watch them to ensure that they are doing it properly.
- Your office can provide dated medication schedules to help confused patients. Suggest linking medications to habitual daily activities.
- Simplify drug regimens as much as possible through once daily medications and combination drugs.
- Local support groups should be offered to patients to help them cope with glaucoma and to exchange ideas on how to use their medications.
- Table 30.3 provides ideas to help augment patient compliance.

References

1. Berg JS, Dischler J, Wagner DJ, Raja JJ, Palmer-Shevlin N. Medication compliance: a healthcare problem. Ann Pharmacother. 1993;27 Suppl 9:S1–24.
2. Dawn AG, Santiago-Turla C, Lee PP. Patient expectations regarding eye care focus group results. Arch Ophthalmol. 2003;121:762–8.
3. Friedman DS, Quigley HA, Gelb L, et al. Using pharmacy claims data to study adherence to glaucoma medications: methodology of the glaucoma adherence and persistence study (GAPS). Invest Ophthalmol Vis Sci. 2007;48:5052–7.
4. Herndon LW, Brunner TM, Rollins JN. The glaucoma research foundation patient survey: patient understanding of glaucoma and its treatment. Am J Ophthalmol. 2006;141:S22–7.
5. Jackevicius CA, Mamdani M, Tu JV. Adherence in statin therapy in elderly patients with and without acute coronary syndrome. JAMA. 2002;288:462–7.
6. Kass MA, Heuer DK, Higginbotham EJ, For Ocular Hypertension Treatment Study Group, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):701–13.
7. Kass MA, Meltzer DW, Gordon M, et al. Compliance with topical pilocarpine treatment. Am J Ophthalmol. 1986;101:515–23.
8. Kosoko O, Quigley HA, Vitale S, et al. Risk factors for non-compliance with glaucoma follow-up visits. Ophthalmology. 1998;105:2105–11.
9. Levy G, Zamacona MK, Jusko WJ. Developing compliance instructions for drug labeling. Clin Pharmacol Ther. 2000;68:586–91.
10. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother. 2002;36:1331–6.
11. Nordstrom B, Friedman D, Mozaffari E, Quigley H, Walker A. Persistence and adherence with topical glaucoma therapy. Am J Ophthalmol. 2005;140:598–606.
12. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–95.
13. Owsley C, McGwin G, Scilley K, et al. Perceived barriers to care and attitudes about vision and eye care: focus groups with older African Americans and eye care providers. Invest Ophthalmol Vis Sci. 2006;47:2797–802.
14. Patel SC, Spaeth GL. Compliance in patients prescribed eyedrops for glaucoma. Ophthalmic Surg. 1995;26:233–6.
15. Reardon G, Schwartz GF, Mozaffari E. Patient persistency with topical ocular hypotensive therapy in a managed care population. Am J Ophthalmol. 2004;137 Suppl 1:S3–12.
16. Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health Syst Pharm. 2001;58:1126–32.
17. Sloan FA, Brown DS, Carlisle ES, et al. Monitoring visual status: why patients do or do not comply with practice guidelines. Health Serv Res. 2004;39:1429–48.
18. Stewart WC, Konstas AG, Pfeiffer N. Patient and ophthalmologist attitudes concerning compliance and dosing in glaucoma treatment. J Ocul Pharmacol Ther. 2004;20:461–9.
19. Tsai JC, McClure CA, Ramos SE, Schlundt DG, Pichert JW. Compliance barriers in glaucoma: a systematic classification. J Glaucoma. 2003;12:393–8.

Medical Treatment: Alternative Medicine and Glaucoma

31

Louis R. Pasquale

Core Messages

- When patients inquire about the relationship between lifestyle factors and glaucoma the physician should seize upon this interaction to educate them about their disease.
- Any alternative treatment for glaucoma should, at the very least, do no harm and not detract from conventional measures to manage the condition.
- There may be activities to avoid for glaucoma patients, although more work is needed to determine if these activities predispose to glaucoma or contribute to the progression of the preexisting disease.
- The Ocular Hypertension Treatment Study is the only trial that demonstrates the efficacy of a strategy to primarily prevent primary open-angle glaucoma (POAG). There are no other proven alternative strategies to prevent the development of POAG.
- There are four randomized controlled trials, including one masked, placebo-controlled study (the United Kingdom Glaucoma Treatment Study) that demonstrate the efficacy of various intraocular pressure-lowering strategies to favorably alter the natural history of open-angle glaucoma (OAG).
- A small placebo-controlled study demonstrated that oral administration of black currant anthocyanins resulted in less visual field loss for OAG after 2 years. More research is needed regarding the relation between dietary bioflavonoid intake and OAG.

31.1 Is There Anything the Patient Can Do to Improve the Outcome of Their Disease Besides Using Conventional Treatments (Medications and Surgery)?

When patients ask this question, view it as an opportunity to bond with them. Do not dismiss the question in a trivial manner. Such a question typically comes from newly diagnosed glaucoma patients who are in the initial phases of acquiring knowledge about their condition and learning about you, the physician. The question is usually

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not meant to challenge your knowledge about glaucoma. Use this question as a stepping-stone to explain the natural history of glaucoma and what one can expect from conventional therapy. If the patient senses an aloof approach from you, how will they respond if you actually recommend something invasive like filtration surgery, even when such a recommendation is totally appropriate? Glaucoma is a life-long condition and providing knowledgeable answers to this question will go a long way toward building a healthy patient–physician relationship.

When considering your response to this question, realize that you cannot dismiss an alternative therapy that a patient may inquire about simply because there is scant data that addresses the question. Rather, structure a response in the context of randomized clinical trials (RCTs) that assess the role of conventional therapy vs. observation in glaucoma. The Ocular Hypertension Treatment Study is the only RCT that assesses whether a specific strategy (lowering intraocular pressure [IOP]) prevents glaucoma and this study was performed in a population that was at high risk for developing POAG by virtue of having elevated IOP at baseline [1]. The European Glaucoma Prevention Study was the only other glaucoma primary prevention trial and it was placebo-controlled. It showed that when IOP lowering was limited to a specific agent (dorzolamide 2 %), one could not prevent POAG among patients with ocular hypertension [2].

RCTs that assessed the role of conventional therapy in retarding disease progression include the Collaborative Normal Tension Glaucoma Study [3] and the Early Manifest Glaucoma Trial [4]. Collectively these two studies showed that lowering IOP with medicine, laser trabeculoplasty, or incisional surgery favorably alters the natural progression of OAG that occurred across a spectrum of IOP. The United Kingdom Glaucoma Treatment Study is the only masked trial demonstrating that conventional therapy (daily latanoprost use) prevented disease progression better than placebo in OAG [5]. The Low Pressure Glaucoma Treatment Study reported that topical brimonidine use was superior to timolol in preserving visual field progression in a group of normal tension glaucoma patients [6]. The other glaucoma RCTs assessed if one form of IOP-lowering therapy was superior to another in the management of the disease (the relevant trials include The Glaucoma Laser Trial [7], The Advanced Glaucoma Intervention Study [8], and The Collaborative Initial Glaucoma Treatment Study [9]).

There is a one RCT using alternative therapy in OAG. Researchers in Korea randomized OAG patients to receive 50 mg/day black currant anthocyanin pills versus placebo in conjunction with conventional therapy [10]. Black currant anthocyanins are a bioflavonoid subclass (blue berries are a major source of anthocyanins) that may improve endothelial cell function in glaucoma [11]. After 2 years, patients receiving back currant anthocyanins had lower mean defects on visual field testing compared to those receiving placebo. This was a small study and more work is needed to assess the role of bioflavonoid intake in glaucoma.

To further explore the issues surrounding lifestyle behaviors that affect the glaucomatous process, one must consider activities that elevate IOP and theoretically worsen disease outcome. Patients rarely look at lifestyle issues and glaucoma from this perspective. It is reasonable for clinicians to be aware of lifestyle activities that elevate IOP, understand the magnitude and duration of their ocular hypertensive effect and their potential impact on glaucoma. For example, playing high wind musical instruments that require the generation of high intrathoracic pressures can produce a doubling of IOP in less than 1 min [12, 13]. Luckily IOP returns to baseline just as quickly after playing ceases. Nonetheless, it is theoretically possible that if someone plays an instrument such as the saxophone regularly for prolonged time periods, a clinically significant increase in IOP could result. While there is no strong evidence that playing these instruments predisposes to glaucoma, it is reasonable to alert glaucoma patients who happen to play these instruments of this effect, particularly if the patient is developing progressive disease at seemingly normal IOP.

Along a similar theme, certain yoga exercises that place the eye below the heart can cause a

doubling of IOP [9]. As soon as the subject assumes a normal posture the IOP returns to baseline. Many glaucoma specialists have anecdotally noted cases of "normal tension glaucoma" in which a careful history revealed frequent performance of inverted position yoga exercises. These anecdotes are supported by published reports of glaucoma progression among yoga practitioners, summarized in a literature synthesis on adverse effects associated with selected yoga exercises [14]. Figure 31.1 illustrates the documentation of an IOP rise during a shoulder stand performed by a yoga instructor. This particular patient sought an alternative medical opinion to confirm a diagnosis of "normal tension glaucoma." In the seated position, her IOP was 10 mmHg OU, but it increased to 50 mmHg OU while assuming an inverted position. Ophthalmic examination revealed glaucomatous cupping and corresponding visual field deficits. Upon initiating bimatoprost nightly, IOP with inverted posture was in the mid-twenties and there was no progressive optic nerve or visual field change after 4 years of follow-up. While the well-documented effect of increased IOP with an inverted posture and case reports suggesting visual field worsening in yoga practitioners are intriguing, observational studies linking inverted yoga exercises and POAG are lacking. However, it pays to warn glaucoma patients about IOP elevations that are associated with inverted posture positions. Furthermore, physicians should consider prolonged performance of such activities as an occasional cause of "normal tension glaucoma" or disease progression despite seemingly excellent IOP control.

Caffeine (1,3,7-trimethylxanthine) is a commonly ingested CNS stimulant that is generally regarded as safe by the Food and Drug Administration (FDA). Caffeine is consumed by a high percentage of the general public and there is generally a fairly wide spread of overall consumption reported in the general population. Caffeine is an adenosine receptor antagonist and adenosine receptors are involved in aqueous humor dynamics [15, 16]. Most studies [17–22] with some exceptions [23, 24] demonstrate that after caffeine consumption from

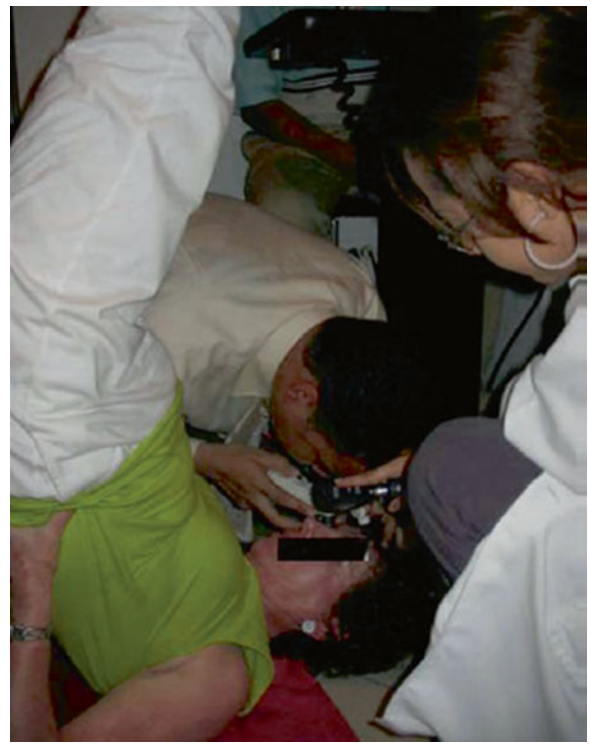

Fig. 31.1 IOP measurement with a Perkins tonometer in a yoga instructor with presumed "normal tension glaucoma." This patient sought several opinions regarding glaucoma before it was discovered that she was a yoga instructor. IOP while seated was 10 mmHg but rose to 50 mmHg during inverted posture. Treatment with medical therapy blunted the IOP during head down posture positions (case courtesy of Dr. Oscar Albis, Asociación para Evitar la Ceguera en México)

beverages such as caffeinated coffee there is a modest increase of IOP (~1–2 mmHg) that lasts for about 2 h. In large prospective analyses, suggestive trends between heavy caffeinated coffee consumption and both POAG and exfoliation glaucoma were reported [25, 26]. Overall, it is reasonable for glaucoma patients to consider curtailing their coffee consumption but more study is needed in this area.

Summary for the Clinician

- When patients ask about alternative therapies for their glaucoma it should be looked upon as an opportunity to educate the patient about their disease.
- Certain lifestyle choices—playing high-resistance wind instruments, assuming certain yoga postures, and consuming large quantities of caffeinated coffee—may adversely affect IOP.

31.2 When a Patient Asks About the Effect of Lifestyle on Glaucoma, How Can I Answer?

There are many studies regarding how specific lifestyle factors (exercise, smoking alcohol, and diet) affect IOP and there are some high quality cross-sectional and prospective studies that assess the relationship between selected lifestyle behaviors and OAG. Indisputably IOP is a strong risk factor for OAG and modifying IOP with conventional therapy can alter the natural course of the disease. An objective in addressing patient-related questions regarding lifestyle and glaucoma is to be generally knowledgeable of the literature regarding the relationship between specific lifestyle behaviors, IOP, and glaucoma. Of course, in the absence of clinical trials, one needs to be cautious about the conclusions that can be reached from such observational studies. The literature for each of these lifestyle activities is summarized briefly below. Also specific recommendations regarding these activities in glaucoma are provided based on the existing evidence.

31.2.1 Exercise

Patients with glaucoma will frequently ask whether aerobic exercise is "good for glaucoma." There is strong evidence that aerobic exercise lowers IOP [27–31]. Furthermore, people who were more conditioned due to regular strenuous activity had IOPs that were 2 mmHg lower than their sedentary counterparts [32]. Isometric exercise like lifting weights may produce modest IOP increases during exertion (average increase: 4 mmHg) [33] that is followed by smaller declines in IOP after exercise is completed [34]. In a cohort of >29,000 runners, every kilometer/day of running was associated with a 6 % reduced risk of self-reported physician diagnosed glaucoma after 7 years of follow-up [35]. Overall, moderate aerobic exercise has many health benefits and should be encouraged. Physicians often wonder if exercise will induce significant IOP elevation in pigmentary glaucoma patients, but the literature suggests this concern is not supported [36, 37]. Of course, if a pigmentary glaucoma patient reports symptoms consistent with an IOP spike after exercise (such as seeing halos around lights), then check the IOP soon after the patient engages in a simulated activity that seems to induce ocular symptoms.

31.2.2 Smoking

Acutely after smoking cigarettes, IOP does not increase appreciably [38]. Glaucoma patients who smoke have been reported to have only slightly higher IOP than glaucoma patients who do not smoke [39]. Cross-sectional and prospective studies on the relationship between cigarette smoking and POAG are mixed, but in the aggregate these studies do not suggest that

smoking increases the risk of glaucoma [40–43]. Nonetheless, there may be an indirect deleterious relation between cigarette smoking and glaucoma. For example, smokers were less likely than nonsmokers to present for a free follow-up confirmatory glaucoma exam after being earmarked as a suspect during a glaucoma screening [44]. The Collaborative Initial Glaucoma Treatment Study found that among OAG patients randomized to the trabeculectomy first arm of the study, smokers had a higher IOP than their nonsmoking counterparts after 9 years of follow-up [45].

In addition to increasing the risk of lung cancer, cigarette smoking is also linked to cataract [46] and age-related macular degeneration [47]. Overall, cigarette smoking increases the risk of vision loss, so all physicians should encourage people to quit smoking. There is strong evidence that engaging patients in smoking cessation programs generally improves health outcomes [48, 49].

31.2.3 Alcohol Consumption

Alcohol consumption causes a dose related reduction in IOP that can last several hours [30, 50–53]. The mechanism is not clear but may involve a temporary osmotic effect [51, 54]. Nonetheless, some studies suggest that regular consumers of alcohol have higher IOP than those who abstain from alcohol use [55–57]. Several observational studies of the relationship between alcohol consumption and POAG have been performed with one study finding an inverse relationship [58], others finding no association [39, 40, 59, 60], while another supported the notion that alcohol consumption is positively associated with POAG [61]. Consuming one alcoholic drink per day may have some cardiovascular benefits [62] but gastroenterologists recommend abstinence to prevent digestive diseases related to alcohol consumption [63]. Thus, it is important to dissuade the notion that drinking alcohol will reduce the risk of glaucoma as the preponderance of existing evidence suggests that drinking alcohol does not have any major association with glaucoma.

31.2.4 Diet

Theoretically, diet could influence the glaucomatous process by altering IOP, changing optic nerve blood flow, or by effecting retinal ganglion cell apoptosis. There is considerable interest in dietary antioxidants because oxidative stress may induce damage to the outflow channel as well as the optic nerve (reviewed by Kumar and Agarwal [64]). No strong relationships were detected between dietary antioxidant intake and the development of POAG, although protective effects from specific foods are possible [65–67]. In a study involving a health professionals group, a statistically significant trend for a protective effect of tea consumption (which is high in bioflavonoid content) was noted [25]. Also, a small placebo-controlled study demonstrated that oral administration of black currant anthocyanins resulted in less visual field loss for OAG after 2 years [10]. Certainly more study is needed regarding antioxidant intake and glaucoma, as the discovery of novel antioxidants that may favorably alter the course of POAG would be most welcome. Nevertheless, at this time one cannot promote antioxidant intake as a strategy to prevent POAG or slow its progression.

Kang et al. [68] proposed that dietary fats might influence IOP by altering the availability of endogenous *n*-6 polyunsaturated fatty acids, which serves as a precursor for prostaglandin $F_{2\alpha}$. Prostaglandin $F_{2\alpha}$ lowers IOP by increasing uveoscleral outflow. Figure 31.2 depicts how the essential fatty acids (linoleic acid and linolenic acid) compete as substrate for ocular enzymes in the formation of prostaglandin $F_{2\alpha}$ and other compounds. Using data from the Nurses Health Study and Health Professionals Follow-up Study, it was reported that a diet with high *n*-6 to *n*-3 polyunsaturated fatty acid ratio was associated with a reduced risk of POAG. Presumably the *n*-6 and *n*-3 fatty acids compete for endogenous enzymes in a manner that favors the accumulation of prostaglandin $F_{2\alpha}$. It should be mentioned that basic science evidence suggests that *n*-3 polyunsaturated fatty acids may be more favorable for ameliorating the glaucomatous process [69, 70]. All in all, the relationship between dietary fat and glaucoma remains unclear.

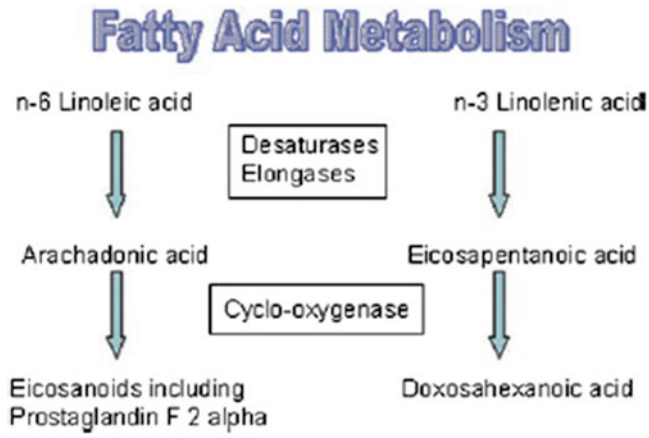

Fig. 31.2 Simplified overview of fatty acid metabolism whereby the essential fatty acids (linoleic acid of the *n*-6 series and linolenic acid of the *n*-3 series) compete as substrate for enzymes that ultimately convert these compounds to eicosanoids that include prostaglandin $F_{2\alpha}$ and docosahexaenoic acid. A diet with a high *n*-6 to *n*-3 ratio (such as exists in diets high in peanut oils) would favor eicosanoid formation and perhaps a lower intraocular pressure (IOP) because of increased prostaglandin F_2 formation with enhanced uveoscleral outflow

Summary for the Clinician

- Aerobic exercise results in lower IOP and has other health benefits, and should be encouraged.
- Alcohol consumption results in lower IOP but observational studies are mixed regarding the relationship between alcohol consumption and POAG. Alcohol consumption should not be encouraged as a means to favorably alter the course of POAG.
- Currently, there are no dietary recommendations that can be made for the glaucoma patient.

31.3 How Should I Counsel Patients Who Inquire Regarding Alternative and Complementary Therapies?

Alternative and complementary therapies (ACT) for glaucoma refer to disease management strategies other than pharmaceutical, laser, or surgical treatments known to lower IOP (referred to as conventional therapy). Surveys of glaucoma patients indicate that between 5 and 11 % use ACT, with a considerable proportion not disclosing such use to their treating ophthalmologist [71, 72]. Patients who resorted to this practice tended to be actively working and were educated beyond the high school level. From the patient's perspective, interest in ACT for glaucoma may stem from attaining a sense of control over a seemingly elusive disease, which initially has no symptoms but could potentially produce blindness. Alternative approaches that truly modify the natural history of glaucoma would provide valuable clues that could one day lead to a better understanding of the disease and a more rationale therapy, so they should not be dismissed. When counseling patients, it is important to emphasize that ACT should not interfere with or serve as a substitute for conventional treatment. Specific forms of ACT for glaucoma are discussed below.

31.3.1 Marijuana Use

Patients frequently ask whether marijuana (or medical cannabis) use represents a reasonable option for treating glaucoma. As of this writing, marijuana use for medicinal purposes is legal in many states but remains illegal under the Federal Controlled Substances Act of 1970; nonetheless, federal authorities have signaled that they will not seek to interfere with medical care providers, dispensaries, and users who are in compliance with state laws. Since federal law does not completely endorse medical marijuana, the FDA does not serve as a conduit to explore optimum dosage, routes of administration, or as an arbiter on

labeling for safety and efficacy. The imbalance between federal and state law creates a void where meaningful research to discern the position, if any, for medical marijuana in glaucoma management is unavailable. It also results in variable oversight of quality control with respect to dispensing marijuana.

The putative active ingredient in marijuana (delta-9-tetrahydrocannabinoid) binds cannabinoid receptors in the ciliary body and results in lower IOP via reduced aqueous humor production [73, 74]. However, the duration of IOP lowering associated with marijuana use is relatively short [75]. In addition to the active ingredient, there are a myriad of other compounds in marijuana smoke and some of these are known carcinogens. Furthermore the ocular side effects of marijuana use are not well known. Overall, the existing evidence suggests that marijuana use for glaucoma is not a feasible management option and it may actually do harm. For these reasons the American Glaucoma Society and the Canadian Ophthalmological Society issued statements recommending against medical marijuana in the treatment of glaucoma [76, 77]. Nevertheless, there may be special cases where selected end-users find the right balance between IOP-lowering effects and drug side effects that preserve sight when all conventional options to lower IOP have been exhausted. Finally, the discovery that marijuana mediates its ocular hypotensive effect via binding of bioactive cannabinoids with specific receptors in the ciliary body offers the opportunity for pharmaceutical researchers to develop safe and effective synthetic cannabinoids in the treatment of glaucoma, although such opportunities have not yet been realized.

31.3.2 Gingko Biloba

The main components of the gingko leaf extract are flavonoid glycosides and terpene lactones. The potential benefits of gingko biloba are believed to be multiple and include neuroprotection, cardio protection, memory enhancement, and anticancer. Gingko is thought to mediate its effects via several biological mechanisms including antiplatelet action, vasodilation, and antioxidant effect. It is understandable that interest in gingko biloba use for glaucoma is high since there is a suggestion in the lay media that gingko has potential as an all-purpose antiaging agent. There is a considerable body of literature published about the effect of gingko on cognitive impairment. A meta-analysis of RCTs found that 240 mg per day of the standardized gingko biloba extract EGb761 produced favorable changes in cognition scores after 22–26 weeks of treatment [78]. This review did not uncover any safety concerns associated with gingko use. Placebo-controlled RCTs regarding the effects of gingko biloba on preexisting visual field loss in normal tension glaucoma patients are contradictory [79, 80]. However, these studies assessed the effects of 120 mg/day and not the dose that seemed to improve cognition in patients with cognitive impairment (240 mg/day) [78]. Thus, use of gingko biloba need not be discouraged but it should not be a substitute for conventional glaucoma therapy.

31.3.3 Bilberry

Bilberry refers to shrubs that yield a fruit resembling blueberries. They can be eaten fresh or made into jams, juices or serve as ingredients for pies. Less is known about bilberry than gingko as a medicinal agent. Bilberry extracts contain high quantities of anthocyanin, a flavonoid with antioxidant properties. As indicated earlier, there is some encouraging evidence that anthocyanins may have some beneficial effects on glaucoma. While bilberry consumption seems perfectly safe, some studies on the effect of bilberry on glaucoma would be useful.

31.3.4 Acupuncture

There is no well-articulated hypothesis about why acupuncture should be beneficial in glaucoma. A Cochrane review completed in 2013 concluded that there is little useful data regarding the effect of acupuncture on glaucoma [81]. Patients should be counseled regarding the

paucity of high quality evidence on the use of acupuncture in glaucoma.

Summary for the Clinician

- Marijuana use does not represent a viable management option for most glaucoma patients.
- More data is needed regarding the effect of gingko biloba and acupuncture on glaucoma.

References

1. Kass MA, Heuer DK, Higginbotham EJ, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120: 701–13.
2. Miglior S, Zeyen T, Pfeiffer N, et al. Results of the European glaucoma prevention study. Ophthalmology. 2005;112:366–75.
3. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Am J Ophthalmol. 1998;126: 487–97.
4. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. Ophthalmology. 2002;120:1268–79.
5. Garway-Heath DF, Crabb DP, Bunce DP, et al. Latanoprost for the treatment of open-angle glaucoma (UKGTS): a randomized, multicenter, placebo-controlled trial. Lancet. 2014;385(9975):1295–304.
6. Krupin T, Liebmann JM, Greenfield DS, et al. A randomized trial of brimonidine versus timolol in preserving visual function: results from the low-pressure glaucoma treatment study. Am J Ophthalmol. 2011; 151:672–81.
7. The Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT): 2. Results of argon laser trabeculoplasty versus topical medicines. Ophthalmology. 1990;97:1403–13.
8. The Advanced Glaucoma Intervention Study (AGIS): 4. Comparison of treatment outcomes within a race. Seven-year results. Ophthalmology. 1998;105: 1146–64.
9. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the collaborative initial glaucoma treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108:1943–53.
10. Ohguro H, Ohguro I, Tanaka S. Two-year randomized, placebo-controlled study of black currant anthocyanins on visual field in glaucoma. Ophthalmologica. 2012;228:26–35.
11. Yoshida K, Ohguro I, Ohguro H. Black currant anthocyanins normalized abnormal levels of serum concentrations of endothelin-1 in patients with glaucoma. J Ocul Pharmacol Ther. 2013;29:480–7.
12. Schuman JS, Massicotte EC, Connolly S, et al. Increased intraocular pressure and visual field defects in high resistance wind instrument players. Ophthalmology. 2000;107:127–33.
13. Schmidtmann G, Jahnke S, Seidel EJ, et al. Intraocular pressure fluctuations in professional brass and woodwind musicians during common playing conditions. Graefes Arch Clin Exp Ophthalmol. 2011;249:895–901.
14. Cramer H, Krucoff C, Dobos G. Adverse events associated with yoga: a systematic review of published case reports and case series. PLoS One. 2013;8(10), e75515.
15. Fleischhauer JC, Mitchell CH, Stamer WD, et al. Common actions of adenosine receptor agonists in modulating human trabecular meshwork cell transport. J Membr Biol. 2003;193:121–36.
16. Karl MO, Fleischhauer JC, Stamer WD, et al. Differential P1-purinergic modulation of human Schlemm's canal inner-wall cells. Am J Physiol Cell Physiol. 2005;288:C784–94.
17. Peczon JD, Grant WM. Sedatives, stimulants, and intraocular pressure in glaucoma. Arch Ophthalmol. 1964;72:178–88.
18. Ajayi OB, Ukwade MT. Caffeine and intraocular pressure in a Nigerian population. J Glaucoma. 2001;10:25–31.
19. Avisar R, Avisar E, Weinberger D. Effect of coffee consumption on intraocular pressure. Ann Pharmacother. 2002;36:992–5.
20. Higginbotham EJ, Kilimanjaro HA, Wilensky JT, et al. The effect of caffeine on intraocular pressure in glaucoma patients. Ophthalmology. 1989;96:624–6.
21. Okimi PH, Sportsman S, Pickard MR, Fritsche MB. Effects of caffeinated coffee on intraocular pressure. Appl Nurs Res. 1991;4:72–6.
22. Jiwani AZ, Rhee DJ, Brauner SC, et al. Effect of caffeinated coffee consumption on intraocular pressure, ocular perfusion pressure and ocular pulse amplitude: a randomized controlled trial. Eye (Lond). 2012;26:1120–30.
23. Ricklefs G. Studies on the ways of life of glaucoma patients. Doc Ophthalmol. 1968;25:43–99.
24. Ricklefs G. Effect of caffeine containing tablets and Coca-Cola on the intraocular pressure of patients without glaucoma and patients with regulated glaucoma. Klin Monbl Augenheilkd. 1969; 154:546–51.
25. Kang JH, Willett WC, Rosner BA, et al. Caffeine consumption and the risk of primary open-angle

glaucoma: a prospective cohort study. Invest Ophthalmol Vis Sci. 2008;49:1924–31.
26. Pasquale LR, Wiggs JL, Willett WC, Kang JH. The relationship between caffeine and coffee consumption and exfoliation glaucoma and glaucoma suspect: a prospective study in two cohorts. Invest Ophthalmol Vis Sci. 2012;53:6427–33.
27. Marcus DF, Krupin T, Podos SM, et al. The effect of exercise on intraocular pressure. I. Human beings. Invest Ophthalmol. 1970;9:749–52.
28. Sargent RG, Blair SN, Magun JC, et al. Physical fitness and intraocular pressure. Am J Optom Physiol Opt. 1981;58:460–6.
29. McDaniel DR, Tribbey CL, Tobias GS. Effects of moderate exercise on intraocular pressure. Am J Optom Physiol Opt. 1983;60:154–7.
30. Buckingham T, Young R. The rise and fall of intraocular pressure: the influence of physiological factors. Ophthalmic Physiol Opt. 1986;6:95–9.
31. Passo MS, Goldberg L, Elliot DL, et al. Exercise training reduces intraocular pressure among subjects suspected of having glaucoma. Arch Ophthalmol. 1991;109:1096–8.
32. Qureshi IA, Wu XD, Xi XR, et al. Resting intraocular pressure of steel factory workers is related to their physical fitness. Ind Health. 1997;35:259–63.
33. Vieira GM, Oliveira HB, de Andrade DT, et al. Intraocular pressure variation during weight lifting. Arch Ophthalmol. 2006;124:1251–4.
34. Chromiak JA, Abadie BR, Braswell RA, et al. Resistance training exercises acutely reduce intraocular pressure in physically active men and women. J Strength Cond Res. 2003;17:715–20.
35. Williams PT. Relationship of incident glaucoma versus physical activity and fitness in male runners. Med Sci Sports Exerc. 2009;41:1566–72.
36. Smith DL, Kao SF, Rabbani R, et al. The effects of exercise on intraocular pressure in pigmentary glaucoma patients. Ophthalmic Surg. 1989;20: 561–7.
37. Haynes WL, Johnson AT, Alward WL. Effects of jogging exercise on patients with the pigmentary dispersion syndrome and pigmentary glaucoma. Ophthalmology. 1992;99:1096–103.
38. Tamaki Y, Araie M, Nagahara M, et al. The acute effects of cigarette smoking on human optic nerve head and posterior fundus circulation in light smokers. Eye (Lond). 2000;14(Pt 1):67–72.
39. Lee AJ, Rochtchina E, Wang JJ, et al. Does smoking affect intraocular pressure? Findings from the Blue Mountains eye study. J Glaucoma. 2003;12:209–12.
40. Klein BE, Klein R, Ritter LL. Relationship of drinking alcohol and smoking to prevalence of open-angle glaucoma. The Beaver Dam Eye Study. Ophthalmology. 1993;100:1609–13.
41. Wilson MR, Hertzmark E, Walker AM, et al. A case-control study of risk factors in open angle glaucoma. Arch Ophthalmol. 1987;105:1066–71.
42. Quigley HA, West SK, Rodriguez J, et al. The prevalence of glaucoma in a population-based study of Hispanic subjects: Proyecto VER. Arch Ophthalmol. 2001;119:1819–26.
43. Kang JH, Pasquale LR, Rosner BA, et al. Prospective study of cigarette smoking and the risk of primary open-angle glaucoma. Arch Ophthalmol. 2003;121: 1762–8.
44. Gwira JA, Vistamehr S, Shelsta H, et al. Factors associated with failure to follow up after glaucoma screening: a study in an African American population. Ophthalmology. 2006;113:1315–9.
45. Musch DC, Gillespie BW, Niziol LM, et al. Factors associated with intraocular pressure before and during 9 years of treatment in the collaborative initial glaucoma treatment study. Ophthalmology. 2007;115:927–33.
46. Ye J, He J, Wang C, et al. Smoking and risk of age-related cataract: a meta-analysis. Invest Ophthalmol Vis Sci. 2012;53:3885–95.
47. Chakravarthy U, Wong TY, Flecther A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis. BMC Ophthalmol. 2010;10:31.
48. Iestra JA, Kromhout D, van der Schouw YT, et al. Effect size estimates of lifestyle and dietary changes on all-cause mortality in coronary artery disease patients: a systematic review. Circulation. 2005;112: 924–34.
49. Wen CP, Cheng TY, Lin CL, et al. The health benefits of smoking cessation for adult smokers and for pregnant women in Taiwan. Tob Control. 2005;14 Suppl 1:i56–61.
50. Peczon J, Grant W. Glaucoma, alcohol, and intraocular pressure. Arch Ophthalmol. 1965;73:495–501.
51. Houle RE, Grant WM. Alcohol, vasopressin, and intraocular pressure. Invest Ophthalmol. 1967;6:145–54.
52. Giurlani BP, Obie LG, Petersen CG, et al. Alcohol and open angle glaucoma-influence on detection, IOP, BP/IOP ratios. J Am Optom Assoc. 1978;49:409–16.
53. Harris A, Swartz D, Engen D, et al. Ocular hemodynamic effects of acute ethanol ingestion. Ophthalmic Res. 1996;28:193–200.
54. Leydhecker W, Krieglstein GK, Uhlich E. Experimental investigations on the mode of action of alcoholic liquor on the intraocular pressure (author's transl). Klin Monbl Augenheilkd. 1978;173:75–9.
55. Leske MC, Warheit-Roberts L, Wu SY. Open-angle glaucoma and ocular hypertension: the long island glaucoma case-control study. Ophthalmic Epidemiol. 1996;3:85–96.
56. Lin HY, Hsu WM, Chou P, et al. Intraocular pressure measured with a noncontact tonometer in an elderly Chinese population: the Shihpai Eye Study. Arch Ophthalmol. 2005;123:381–6.
57. Yoshida M, Ishikawa M, Kokaze A, et al. Association of life-style with intraocular pressure in middle-aged and older Japanese residents. Jpn J Ophthalmol. 2003;47:191–8.
58. Kang JH, Willett WC, Rosner BA, et al. Prospective study of alcohol consumption and the risk of primary open-angle glaucoma. Ophthalmic Epidemiol. 2007; 14:141–7.

59. Fan BJ, Leung YF, Wang N, et al. Genetic and environmental risk factors for primary open-angle glaucoma. Chin Med J (Engl). 2004;117:706–10.
60. Leske MC, Connell AM, Wu SY, et al. Risk factors for open-angle glaucoma. The Barbados Eye Study. Arch Ophthalmol. 1995;113:918–24.
61. Kahn HA, Milton RC. Alternative definitions of open-angle glaucoma. Effect on prevalence and associations in the Framingham eye study. Arch Ophthalmol. 1980;98:2172–7.
62. Anthony D, George P, Eaton CB. Cardiac risk factors: environmental, sociodemographic and behavioral cardiovascular risk factors. FP Essent. 2014;421: 16–20.
63. Gonzales JF, Barnard ND, Jenkins DTT, et al. Applying the precautionary principle to nutrition and cancer. J Am Coll Nutr. 2014;33:239–46.
64. Kumar DM, Agarwal N. Oxidative stress in glaucoma: a burden of evidence. J Glaucoma. 2007;16: 334–43.
65. Kang JH, Pasquale LR, Willett W, et al. Antioxidant intake and primary open-angle glaucoma: a prospective study. Am J Epidemiol. 2003;158:337–46.
66. Wang SY, Sing K, Lin SC. Glaucoma and vitamins A, C, and E supplement intake and serum levels in a population-based sample of the United States. Eye (Lond). 2013;27:487–94.
67. Giaconi JA, Yu F, Stone KL, et al. The association of consumption of fruits/vegetables with decreased risk of glaucoma among older African-American women in the study of osteoporotic fractures. Am J Ophthalmol. 2012;154:635–44.
68. Kang JH, Pasquale LR, Willett WC, et al. Dietary fat consumption and primary open-angle glaucoma. Am J Clin Nutr. 2004;79:755–64.
69. Toutas T, Birke MT, Kruse FE, et al. Preventive effects of omega-3 and omega-6 fatty acids on peroxide mediated oxidative stress responses in primary human trabecular meshwork cells. PLoS One. 2012;7:e31340.
70. Nguyen CT, Vingrys AJ, Bui BV. Dietary ω-3 deficiency and IOP insult are additive risk factors for ganglion cell dysfunction. J Glaucoma. 2013;22:269–77.
71. Rhee DJ, Spaeth GL, Myers JS, et al. Prevalence of the use of complementary and alternative medicine for glaucoma. Ophthalmology. 2002;109:438–43.
72. Wan DJ, Daniel S, Kassam F, et al. Survey of complementary and alternative medicine use in glaucoma patients. J Glaucoma. 2012;21:79–82.
73. Porcella A, Maxia C, Gessa GL, et al. The human eye expresses high levels of CB1 cannabinoid receptor mRNA and protein. Eur J Neurosci. 2000;12:1123–7.
74. Flach AJ. Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. Trans Am Ophthalmol Soc. 2002;100:215–22; discussion 222–4.
75. Green K. Marijuana smoking vs. cannabinoids for glaucoma therapy. Arch Ophthalmol. 1998;116:1433–7.
76. Jampel H. American Glaucoma Society position statement: marijuana and the treatment of glaucoma. J Glaucoma. 2010;19:75–6.
77. Buys YM, Rafuse PE. Canadian Ophthalmological Society policy statements on the medical use of marijuana for glaucoma. Can J Ophthalmol. 2010;45:324–6.
78. Tan MS, Yu JT, Tan CC, et al. Efficacy and adverse effects of ginko biloba for cognitive impairment and dementia: a systematic review and meta-analysis. J Alzheimers Dis. 2015;43:589–603.
79. Quaranta L, Bettelli S, Uva MG, et al. Effect of Ginkgo biloba extract on preexisting visual field damage in normal tension glaucoma. Ophthalmology. 2003;110:359–62; discussion 362–4.
80. Guo X, Kong X, Huang R, et al. Effect of ginko biloba on visual field and contrast sensitivity in Chinese patients with normal tension glaucoma: a randomized, crossover clinical trial. Invest Ophthalmol Vis Sci. 2014;55:110–6.
81. Law SK, Li T. Acupuncture for glaucoma. Cochrane Database Syst Rev. 2013;5, CD006030.

Procedural Treatments: Laser Trabeculoplasty

32

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Core Messages

- Differences between trabeculoplasty and medications.
- Advantages of ALT and SLT.
- Techniques of trabeculoplasty.
- Complications of trabeculoplasty.
- Newer methods of laser trabeculoplasty.

32.1 Should Laser Trabeculoplasty or Medication Be Used as First-Line Treatment? How Can Trabeculoplasty Be Used as Adjunctive or Replacement Treatment?

There are two main considerations for using laser trabeculoplasty (LTP) as first line or replacement treatment. There are disease related issues and economic factors. Disease related issues are efficacy, compliance, diurnal IOP control, and side effects/risks. Economic issues are divided into personal financial impact for the individual patient and medical costs for society in general.

32.1.1 What Is the Efficacy of Trabeculoplasty?

LTP has been employed as an initial, adjunct, or replacement therapy to lower intraocular pressure (IOP) in patients with open-angle glaucoma (OAG). The original procedure was described using argon laser (major peaks at 488 and 514 nm). Large prospective studies have shown that argon laser trabeculoplasty (ALT) is a relatively safe and an effective procedure. The Glaucoma Laser Trial showed that in patients with newly diagnosed OAG, ALT was at least as effective as the initial treatment with timolol maleate 0.5 %, even after 7 years [1, 2]. However, ALT produces significant tissue disruption and coagulation damage to the trabecular meshwork, possibly contributing to the limited effectiveness of retreatment [3, 4]. Indeed if the angle is repeatedly treated with argon laser, this will eventually lead to synechial angle-closure and a decrease in outflow facility. This, coupled with the fact that most patients required medications eventually, leads to the failure of ALT's acceptance as primary glaucoma therapy. Most physicians in the United States maintained the algorithm of medication first, possible LTP, and then filtration surgery.

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This treatment algorithm may be changing with the approval of selective laser trabeculoplasty (SLT) by the FDA in 2002 for the treatment of OAG. Using the 532 nm, frequency-doubled, Q-switched Nd:YAG laser, SLT results in the selective absorption of energy by pigmented cells and spares adjacent cells and tissues from thermal energy [5]. Compared to ALT, each SLT pulse delivers less than 0.1 % total energy and is eight orders of magnitude shorter in duration. This results in milder tissue response and the potential for repeated treatment, which has only been shown in a handful of meeting abstracts [6]. SLT is also easier to perform since the area of the laser spot is 64 times larger than that of ALT and large enough to cover the entire width of the trabecular meshwork.

SLT was initially studied as a secondary modality in cases of failure of medical therapy or ALT [7–10]. More recently, SLT has been proven effective as primary treatment in OAG with minimal side effects or complications [11–13]. The non-comparative trials showed an IOP reduction from an untreated baseline of approximately 30 %, sustained for 3–5 years. Two randomized trials of SLT vs. medication as primary therapy were conducted. One study showed an IOP reduction after SLT of 31 % from baseline, which was comparable with the 30.6 % reduction seen with a prostaglandin analog. The other randomized trial (SLT/MED) [14] assigned patients with OAG or OHTN to 360 SLT or medical therapy with prostaglandin analog. The results of the study demonstrated that the reduction in IOP was similar in SLT (6.3 mmHg) vs. medical therapy (7.0 mmHg). Additionally fewer eyes in the SLT group (11 %) needed additional SLT treatment for IOP lowering compared to the medical group (27 %) that needed additional medications although this was not statistically significant.

When studied as adjunctive therapy (additive to medical therapy), the following was noted. Latina et al. [10] treated patients with IOP uncontrolled on maximal medical therapy or with prior failed ALT and found that 70 % of patients responded with a 3 mmHg or more reduction in IOP at 6 months. Replacement studies have focused on the ability to reduce the number of glaucoma medications in medically controlled open-angle glaucoma patients treated with SLT. Francis et al. [15] found that glaucoma medications could be reduced by a mean of 2.1 per patient at 6 months and 1.3 at 12 months when medically controlled glaucoma patients were treated with SLT.

32.1.2 Does Trabeculoplasty Benefit Compliance?

Compliance with medical treatment is a major problem in the field of medicine, and glaucoma is no exception. A study by Nordstrom et al. [16] showed that the majority of glaucoma patients have trouble complying with their prescription regimens. Over 90 % were nonadherent or failed to use medication at various points in time. Nearly 50 % were not persistent, defined as failure to maintain continuous treatment with prescribed medications. The often-quoted study of Kass et al. demonstrates the difficulties of compliance in a glaucoma population [17]. This patient population was using pilocarpine 4 times daily, and unknowingly received a bottle with a microchip sensor attached to monitor dosing. They found that 28–59 % of patients were noncompliant. Furthermore, the patients' perception was that they were compliant with 97 % of their doses. The treating physicians were not able to predict which patients had poor vs. good compliance.

Clearly, LTP addresses the problem of compliance. While it may not be 100 % effective, it has 100 % compliance. The treating physician performs the procedure, and it either works or it does not. Therefore, the procedure has a role to play in noncompliant patients, no matter what the cause of noncompliance. One problem is that some patients will not be completely controlled with LTP alone, and will still need medical therapy and hence be at risk for noncompliance. However, by simplifying their regimen and reducing the number of medications needed, this laser treatment may help with compliance.

32.1.3 How Well Does Trabeculoplasty Control the Diurnal IOP Curve?

The effect of ALT on diurnal IOP was measured by Greenidge et al., who measured IOP over a 24 h period every 2–4 h in the sitting position [18]. This cohort of patients was using maximal medical therapy, including various combinations of pilocarpine, timolol, epinephrine, and oral carbonic anhydrase inhibitors. They found a significant reduction in the mean IOP, peak IOP, and the range of IOP after laser treatment.

A similar study involved diurnal IOP measurements in medically uncontrolled glaucoma patients before and after diode-pumped frequency doubled Nd:YAG laser trabeculoplasty [19]. IOP measurements were taken sitting and supine during the day and supine at night. The authors found a significant reduction in nocturnal mean, peak, and range of IOP, but not in daytime IOP. They concluded that LTP decreased the nocturnal IOP spike and therefore the mean 24 h IOP in open-angle glaucoma patients on maximal medical therapy.

More recently a randomized study evaluated the effect of SLT on IOP control and diurnal tension curves of patients with OAG and OHTN when compared to latanoprost. In this study SLT achieved similar IOP reduction as latanoprost. However, success in fluctuation reduction was 50 % for SLT compared to 83 % for latanoprost [20]. In addition, 360° SLT treatment was noted to be more effective in achieving lower IOP fluctuations when compared to 180° treatment [21].

Thus, we can conclude that LTP can exert an effect on diurnal IOP, with a reduction in 24 h IOP, and nocturnal IOP spikes, even if it does not appear to change the daytime measured IOP. This has implications for normal tension glaucoma patients, or for those patients with IOP that seems to be controlled, but with signs of clinical progression.

32.1.4 What Are the Side Effects/ Risks of Trabeculoplasty?

The risks of LTP are minimal, and mostly occur in the short-term postoperative period. A transient elevation of IOP (IOP spike) occurs in about 5 % of patients and is successfully treated by medications with reduction to near baseline IOP by the first postoperative day. Inflammation and discomfort can occur following the procedure and may last a few days. This is treated with topical NSAIDs or steroids, or simply observed with or without an oral NSAID or analgesic. A recent prospective study analyzed the adverse effects of SLT and determined that there were no adverse effects of SLT in the group of 64 patients [22]. More rare but serious side effects have been noted in the literature and include corneal edema with subsequent thinning and hyperopic shift [23, 24] and cystoid macular edema [25].

The side effects of glaucoma medications are well known and will not be listed here, but include localized ocular, periocular, and systemic effects. The severity of side effects ranges from mildly irritating to life threatening. The risk of medications lasts as long as they are being used. However, the risks are generally small, and therefore similar overall to LTP.

32.1.5 What Are the Economic Issues Involved with Trabeculoplasty?

LTP, which is usually covered by medical insurance, is helpful to the patient in terms of personal finances. Used as initial, replacement, or adjunctive therapy, LTP can save the patient some of the costs of chronic use of glaucoma medications. Additionally, the societal cost of treating glaucoma with medications or LTP has been studied in the Canadian health care system, and was found to be favorably impacted by the use of LTP [26, 27].

Summary for the Clinician

- LTP is effective as initial, replacement, and adjunctive therapy for open-angle glaucoma.
- LTP is useful in addressing compliance problems with chronic use of glaucoma medications.
- LTP is effective in flattening the diurnal IOP curve and decreasing nocturnal IOP spikes.
- LTP may help decrease the cost of medications for the patient.
- LTP may reduce societal costs of treating glaucoma.

32.2 Is There Still a Place for ALT Given the Availability of SLT?

There are several outcome measures that should be compared between ALT and SLT. Foremost is efficacy, reflected in IOP reduction and the length of its effect. Secondary is complication rate, and includes IOP spike, scarring of the angle, inflammation, and patient discomfort. The two lasers also can be compared in terms of ability to retreat and versatility of the laser platform.

32.2.1 What Is the Efficacy of ALT Versus SLT?

A randomized trial of ALT vs. SLT was performed by Damji et al. [7, 8]. ALT was performed in 87 eyes and SLT in 89 eyes with treatment to 180° of the trabecular meshwork, and follow-up was reported for 12 months. The baseline IOP was 23.5 mmHg in the ALT group and 23.8 mmHg in the SLT group. Both groups had a significant reduction in IOP at 12 months, with −6.04 mmHg in the ALT group and −5.86 mmHg in the SLT group. There was no significant difference in IOP reduction at any point of time between the two groups. There were no differences in complications, although they noted a higher incidence of "cellular" reaction in the SLT group 1 h after treatment. This did not translate into a difference in complications, and the cellular reaction was not present at 1 week after treatment.

A longer follow-up comparison was made in a nonrandomized trial by Juzych et al. [9]. This retrospective review studied 154 eyes after ALT and 41 after SLT for up to 5 years with a mean follow-up of 37.4 months for the ALT group and 33.6 months for the SLT group. Both lasers were applied over 180° of trabecular meshwork. Success was defined by criterion [1] as a decrease in IOP of 3 or more mmHg with no additional medications and by criterion [2] with a 20 % or more IOP reduction additionally required. Success rates were similar between the two groups, with 1-, 3-, and 5-year success of 68, 46, and 32 % for SLT (criterion 1) and 54, 30, and 31 % for ALT. By criterion [2], success rates were 58, 38, and 31 % for SLT, and 46, 23, and 13 % for ALT. There was no significant difference in IOP reduction from baseline, or glaucoma medications between groups.

32.2.2 What Are the Complications of ALT Versus SLT?

Both ALT and SLT have a similar incidence of postoperative IOP spike, in the 3–5 % range. No randomized trials have found any difference in this occurrence. However, most clinicians who perform ALT limit treatment to 180° to avoid the higher incidence of IOP spike. Most users perform initial SLT with 360° treatment due to evidence that the incidence of IOP spikes is similar between 180° and 360° treatment [11].

There is good evidence from in vitro studies on human trabecular meshwork showing that argon laser results in a greater amount of scar tissue and coagulative necrosis compared to that seen with the frequency doubled Nd:YAG laser. This has been shown in eye bank eyes [28] and in cultured human trabecular meshwork tissue [3]. This difference has to do with the selective nature of SLT, where only pigment containing cells within the trabecular meshwork take up the laser energy.

Because of the very short pulse duration (compared to thermal relaxation time of the tissue), the adjacent tissues do not take up the laser energy, and the spread of the damage due to heat is minimized. Thus, SLT may cause less tissue damage and fewer anterior synechiae. More importantly, this has implications for retreatment.

32.2.3 How Does Retreatment Compare Between ALT and SLT?

The accepted definition of retreatment with LTP is applying laser to an area that was treated previously. In most circumstances, this will be an initial 360° treatment followed by retreatment of the same 360°. Retreatment is usually applied when an initial treatment has been successful, but the effect has worn off over a period of time. However, it is sometimes applied when the initial response is not great enough to reach the target IOP levels. Treating 180° followed by laser to the remaining 180° should be termed augmentation of treatment. Finally, SLT performed after ALT (or any LTP followed by treatment with a different laser) should be differentiated as sequential treatment with the two laser modalities identified.

Several studies have demonstrated diminishing efficacy with ALT retreatment [29–31, 32]. The theory is that with repeat treatment greater coagulative necrosis of the trabecular meshwork occurs, thus decreasing the amount of surface area available for outflow. As SLT creates minimal tissue damage, it can theoretically be repeated without an appreciable decrease in efficacy. This theory has yet to be proven in published studies, however.

Sequential treatment with SLT after ALT has documented success in several clinical studies. The initial clinical study by Latina et al. [10] included two SLT treatment arms: one group had uncontrolled IOP on maximal medical therapy and the second had uncontrolled IOP with prior failed ALT. A total of 101 patients completed the study, with 56 of those in the prior ALT group. This group had a mean IOP reduction of 3.8 mmHg from a baseline of 25.3 mmHg, which was comparable to the treatment given to the naïve group.

A recent French Study evaluated the efficacy of SLT retreatment in myopes and patients with increased trabecular pigmentation. SLT efficacy was equivalent in the second treatment in all groups; however, in patients with increased pigmentation, IOP response was greater following the second treatment. This suggests that in patients with increased pigmentation, retreatment may be necessary to achieve maximal response [33].

Hong et al. reported data of repeat SLT 360° following initial successful SLT 360 [26]. In this retrospective review, 44 eyes of 35 open-angle glaucoma patients with a prior 360° SLT that was successful for 6 months but eventually lost efficacy were treated with a second 360° SLT. The reduction in IOP after SLT 1 and SLT 2 was not statistically different at any time points, except at 1–3 months, when reduction was greater after SLT 1. Using a definition of success of 20 % or greater IOP reduction, the authors found no difference after SLT 1 and 2. They also did not find any difference whether the SLT was repeated in the first 6–12 months after initial laser, or after 1 year. They concluded that repeat 360° SLT is safe and effective after an initially successful 360° SLT has lost efficacy, and that this may be accomplished as early as 6 months after the initial laser.

32.2.4 How Does the Versatility of the Laser Sources Compare?

The final comparison between the two lasers is versatility of the two machines. Argon laser has many applications as a thermal laser, including LTP, iridoplasty or gonioplasty, pretreatment for iridotomy, pupilloplasty, and retinal laser. SLT is limited to LTP, although one version of the instrument incorporates a 1064 nm wavelength Nd:YAG for use in capsulotomy, membranotomy, lysis of vitreous strands, anterior vitreolysis (of anterior hyaloid face), etc.

Summary for the Clinician

- Efficacy of ALT and SLT is equivalent.
- Complications of ALT and SLT are equivalent.
- SLT results in less scarring of the trabecular meshwork, and may have greater efficacy in retreatment.
- The argon laser platform is more versatile.
- SLT can be performed after ALT failure or after its loss of effect over a period of time.

32.3 When Should SLT or ALT Not Be Performed?

32.3.1 Types of Glaucoma

LTP enhances outflow facility through an intact trabecular outflow pathway. Any form of glaucoma that has an intact trabecular meshwork and Schlemm's canal, even though outflow facility may be reduced, is a candidate for ALT or SLT. Therefore, primary open-angle glaucoma and secondary open-angle glaucomas (exfoliation glaucoma, pigmentary glaucoma) are excellent candidates. Steroid induced glaucoma is a possible candidate, but the indication is not as strong for this type of glaucoma. Laser treatment in uveitic glaucoma may be contraindicated due to a chance of increased posttreatment anterior chamber reaction or peripheral anterior synechiae formation. Any angle-closure glaucoma, primary or secondary, is not a good candidate for LTP, although a narrow angle without iris apposition or synechiae can have its trabecular meshwork treated to improve outflow. Neovascular glaucoma can actually be worsened with LTP, which may act as a stimulus for further neovascularization. Abnormal angles from prior damage as in angle recession glaucoma may not respond predictably to LTP.

32.3.2 IOP Reduction

LTP is indicated as a primary or adjunctive glaucoma treatment, with the expectation of a 20–30 % decrease in IOP. In cases of severe glaucoma damage or low-tension glaucoma where the target IOP is very low or the desired IOP reduction is very large, LTP may not be indicated. Similarly, if a large IOP reduction is desirable immediately, LTP is limited because of the delay of its effect. In these cases, glaucoma filtration surgery may be a more appropriate choice.

32.3.3 Maximal Medical Therapy

Although ALT or SLT can be effective when added to medications, the lowest success rate is seen when on maximum medical therapy. As such, LTP can be considered in the same light as adding a medication. The more medications that are currently being used, the lower the efficacy of additional treatment. However, since LTP works by increasing trabecular aqueous outflow facility, its method of action is not redundant with any of the widely used glaucoma medications, and therefore is theoretically additive to drugs acting on aqueous production or uveoscleral outflow. The only drugs that act in a similar fashion to LTP are the miotic agents such as pilocarpine.

Summary for the Clinician

- LTP is most effective in open-angle glaucomas; it should not be used in neovascular and uveitic glaucomas.
- LTP may not be indicated if a very low IOP target range is necessary.
- IOP reduction is diminished with greater number of adjunctive medications.

32.4 What Are the Laser Settings and Techniques for ALT and SLT?

32.4.1 Argon Laser Trabeculoplasty

The settings for ALT are 50 μm spot size, 0.1 s pulse duration, and power starting at 600 mW. The aiming beam is centered at the junction between the pigmented and nonpigmented trabecular meshwork (at the anterior edge of the pigmented TM), and spaced approximately 3–4 spot sizes apart so that 50 spots are used to cover 180° of the angle. The power is titrated so that slight blanching of the pigmented TM occurs, or until a small bubble formation is seen. If large bubble formation or charring of the TM occurs, the power is too high. Most clinicians favor treating the inferior angle first, because of the greater pigmentation and also to reduce any effect on possible future superior trabeculectomy.

32.4.2 Selective Laser Trabeculoplasty

The settings for SLT are fixed except for the power. The spot size is 400 μm and the pulse duration is 3 ns. The starting power varies depending on the degree of angle pigmentation. In a normally pigmented eye initial power is set at 0.8 mJ, in a highly pigmented angle at 0.6 mJ, and at 1.0 mJ for a relatively nonpigmented angle. The aiming beam is centered on the trabecular meshwork and effectively covers the entire TM with some overlap onto scleral spur and Schwalbe's line. Because of the larger size, the margins of the aiming beam are not in sharp focus. The laser should be calibrated prior to use so that the aiming beam, slit lamp focus, and treating laser are confocal. This can be tested using any pigmented target (such as a piece of paper with dark ink on it). The power is titrated up or down until the treatment end point is reached. The end point consists of small cavitation energy bubbles seen in the aqueous humor proximal to the trabecular meshwork (not within the tissue such as in ALT). These are commonly referred to as "champagne bubbles" and float superiorly after forming. The least amount of energy needed to see these bubbles for a majority of shots is recommended. The power may need to be changed during the procedure if there is significant variation in the trabecular pigment. In highly pigmented angles, such as seen in pigmentary or exfoliation glaucoma, care must be taken not to overtreat—powers as low as 0.3–0.4 mJ are often adequate. In these cases, one may consider treating 180° initially to prevent an IOP spike.

Summary for the Clinician

- ALT settings are 50 μm spot size, 0.1 s duration, and power titrated to tissue effect (blanching of TM).
- SLT settings are 400 μm spot size, 3 ns duration, and power titrated to cavitation bubbles (champagne bubbles).

32.5 What Pearls Are There for Performing ALT and SLT?

I recommend a mirrored goniolens without magnification for LTP, because this ensures that the spot size and power delivered to the angle are not changed by the optics of the lens. Examples are the Goldmann three mirror lens, using the rounded angle mirror, or the Latina lens, or any mirrored goniolens applied with a coupling solution. The Ritch laser trabeculoplasty lens has four mirrors, two of which are nonmagnifying. For a coupling agent, methylcellulose (i.e., Goniosol) is most commonly used, but it tends to be sticky in some patients and can sometimes result in a corneal abrasion as the lens is rotated. An alternative is artificial tear gel (not ointment), which seems to be gentler on the corneal epithelium.

In cases of a narrow angle and poor visibility of the trabecular meshwork, there are several

helpful measures. The first is instillation of low dose pilocarpine (0.5–2 %) 10 min prior to the procedure. This pulls the peripheral iris away from the angle and results in a better view. An easier alternative is to have an assistant shine a light into the contralateral eye. This will result in pupillary miosis via the consensual response and an improved view of the angle. Another trick that can be applied during the procedure is to have the patient move their gaze towards the mirror being used for treatment. For example, if the inferior angle is being treated and the mirror of the goniolens is superior, instruct the patient to look up. This will rotate the eye such that more of the angle is visible in the goniolens. If the angle is so narrow that none of these procedures helps, then the patient probably requires a laser peripheral iridotomy for narrow angle. If the angle remains narrow after iridotomy, then an argon laser iridoplasty can be considered.

One situation that occurs rarely but can cause problems with any laser procedure is the highly anxious patient. Usually these individuals can be identified during the initial exam and also have problems with tonometry and gonioscopy. My practice is to recommend pretreatment with an oral sedative agent prior to attempting laser. Unless there are contraindications (pregnancy, hypersensitivity, obstructive lung disease, depression, drug and alcohol addiction, to name a few), I have found alprazolam (Xanax) to be the most helpful. A prescription for 0.5 mg tablet is written prior to the appointment, and the patient is instructed to take one at the time of check in. An additional dose may be taken if anxiety is still present at the time of laser. Certainly, all precautions must be taken with the use of a psychoactive drug, and the responsibility for judgment rests with the treating physician (Fig. 32.1).

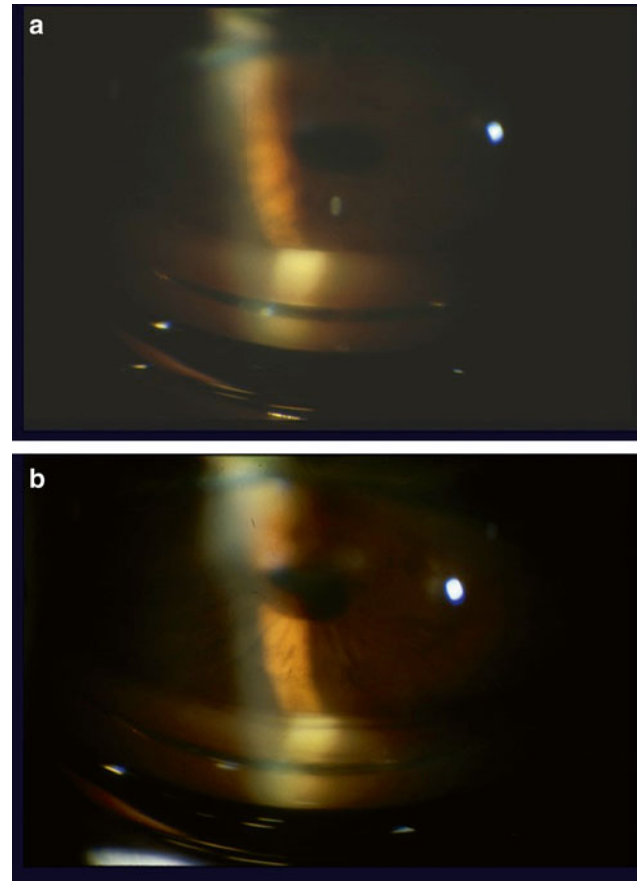

Fig. 32.1 (**a**, **b**) The images represent the technique to tilting the goniolens towards the angle being visualized "over the hill" while performing SLT. When compared to the first image, tilting the lens allows for the angle to be visualized more clearly so that laser energy can be applied to the appropriate target

Summary for the Clinician

- Use a mirrored goniolens without magnification and with a coupling agent.
- Pilocarpine or light in the patient's eye can constrict the pupil and open the angle for better viewing.
- Direct the patient's gaze towards the treating mirror to get a better view of a narrow angle.
- Topical anesthesia should be used, and sometimes oral sedation can be offered to the anxious patient.

32.6 What Complications Can I Expect and How Do I Deal with Them? How Frequently Should a Patient Be Seen in Follow-Up After Trabeculoplasty?

The risks of LTP are minimal with the most common one being an IOP spike. An IOP spike can occur in up to 5 % of individuals and seems to be related to the type of laser used as well as the amount of energy delivered. IOP spikes are almost always transient, most occur within the first hour after laser, and the great majority resolve with medical treatment by the next day. Topical treatment with apraclonidine or brimonidine perioperatively effectively reduces the incidence of this complication. ALT is usually applied over 180° to reduce the incidence of IOP spikes, whereas SLT is increasingly being applied over 360° initially to maximize the IOP reduction. The study by Nagar et al. [11] did not show a significant increase in the incidence of IOP spike after SLT with this full treatment, but did show a dose response in IOP reduction related to the amount of angle treated. The overall incidence of IOP spike may be lower with SLT than with ALT, but both are generally in the 3–5 % range. Anecdotally, the amount of power used seems to be proportional to the frequency of IOP elevation. Thus, the minimum of power necessary to achieve the desired effect is recommended.

The recommended protocol is to check for an IOP spike 1 h after laser. A significant elevation may be defined as an IOP increase of 8 mmHg or more above baseline, but in severe cases of glaucoma a smaller IOP spike may be significant. Treatment may be an additional topical or oral glaucoma medication, depending on the amount of optic nerve damage and visual field loss. Sustained elevation of IOP after LTP is quite rare but has been seen. If this occurs, filtration surgery is sometimes necessary. If an IOP spike is seen, I recommend a follow-up the next day. If no IOP elevation is measured, follow-up can be any time from 1 week to 1 month post procedure. It is important to wait up to 3 months after therapy for the lowering of IOP, as the biological response may take some time to develop and exert its effect on outflow.

Pain and inflammation are possible and may be treated with observation, oral or topical NSAIDs, or topical steroids. Since the cascade to initiate the effect of IOP lowering is linked to initial tissue inflammation, many physicians avoid postoperative topical steroids so as to not blunt this response.

As mentioned previously, ALT can cause peripheral anterior synechiae (or goniosynechiae) and eventually lead to chronic angle-closure. In SLT there is a reduced amount of heat energy absorption but goniosynechiae can still be seen postoperatively.

Summary for the Clinician

- Treat prophylactically for IOP spike.
- Check IOP at 1 h post laser.
- If there is no IOP elevation 1 h post laser, follow-up can be scheduled for 1–4 weeks as per the surgeon's discretion.
- Pain and inflammation can be treated with topical or oral NSAID if needed; however, some surgeons feel that IOP reduction is linked to the inflammatory response and discourage use of these medications.
- It may take up to 3 months to see an IOP lowering effect from the laser treatment.

32.7 What Is the Mechanism of Action of ALT and SLT?

The accepted method of IOP lowering with LTP is an increase in aqueous outflow facility through the trabecular meshwork outflow pathway. However, there is some debate as to how this occurs.

32.7.1 Mechanical Theory

This theory applies mainly to the argon laser as a result of its thermal effects on treated tissues. The electromagnetic energy of the laser is absorbed as heat energy when it contacts the trabecular meshwork, causing a contraction of the tissue and shrinkage of collagen fibers. This results in a stretching of adjacent trabecular meshwork and widening of the spaces between trabecular beams and possible widening of Schlemm's canal. This in turn can lead to an increase in aqueous outflow.

32.7.2 Biologic Theory

This theory can apply to all forms of lasers used for LTP. It suggests that the laser exerts its effects through the induction of a biological cascade of events as a response to tissue injury. ALT causes an increase in macrophage recruitment to the treated site, which results in remodeling of the extracellular matrix and an increase in outflow. Additionally, ALT was shown to upregulate interleukin 1 (IL-1) and tumor necrosis factor (TNF) gene expression, which in turn upregulates matrix metalloproteinase (MMP) expression and a remodeling of the extracellular matrix [34, 35]. This remodeling results in lowering of aqueous outflow resistance.

Further support for the biologic theory comes from Alvarado et al. who irradiated cultured human trabecular meshwork endothelial cells with the SLT laser [36]. The trabecular meshwork endothelial cells were allowed to condition the culture medium, which was then added to Schlemm's canal endothelial cells. A response was observed both by measuring Schlemm's canal endothelial permeability and gene expression. The Schlemm's canal endothelial cells exposed to trabecular meshwork endothelial cell treated medium underwent a fourfold increase in fluid permeability, as well as an increase in differential gene expression. Among the upregulated genes are those for cytokines IL-8, IL-1α, IL-1β, and TNF-α. Adding these cytokines to Schlemm's canal endothelial cells also significantly increased permeability. The summary of this evidence is that trabecular meshwork endothelial cells regulate Schlemm's canal endothelial cell permeability and have a significant role in aqueous outflow regulation. In addition, this regulatory capacity is stimulated by the application of laser energy and cytokine release.

32.7.3 Repopulation Theory

Another proposed mechanism of action for ALT is that the laser energy stimulates increased cell division and repopulation of the trabecular meshwork. Several studies have shown an increase in DNA replication and cell division after argon laser treatment [37–40]. This begins in the anterior nonfiltering tissue of the trabecular meshwork and eventually leads to repopulation of the burn sites. Perhaps this population of cells serves as a source of pluripotent stem cells that can repopulate the trabecular meshwork.

Summary for the Clinician

- Theories of trabeculoplasty mechanism of action include:
  - Mechanical theory of ALT.
  - Biologic theory of LTP (ALT and SLT).
  - Repopulation theory of ALT (may also apply to SLT).

32.8 What Newer Laser Trabeculoplasty Modalities Are on the Treatment Horizon?

32.8.1 Micropulse Laser Trabeculoplasty

Micropulse laser trabeculoplasty (MLT) is a newer technique using the 810 nm diode Iridex IQ810 laser (Iridex Corporation, Mountain View, CA). The goal is to use the micropulsed emission mode with short "on" time followed by a long "off" time to create a sublethal thermal insult to viable cells in the trabecular meshwork. This is thought to minimize heat absorption by the target tissue and consequently reduce collateral thermal damage such as that seen in ALT.

Micropulse settings are approximately 0.3 ms on and 1.7 ms off. The spot size is 300 μm, and 50–60 spots are delivered to cover 180° of the angle. One advantage of the laser is that it has other applications, such as transscleral cyclophotocoagulation, retinal photocoagulation, iridotomy, and perhaps laser suture lysis.

The 1-year results of an Italian pilot study presented at the 2007 International Glaucoma Symposium and 2007 World Glaucoma Congress showed a mean IOP reduction of 22 % in 24 out of 32 eyes with OAG [41]. Additionally a study from Belgium compared 180° treatment in patients with OAG with MLT vs. ALT found that while the MLT group had minimal anterior segment inflammation and good safety profile, its IOP lowering efficacy was not as effective as the ALT group at 3 months follow-up [42]. Another retrospective study reviewed 40 eyes of 29 patients who had undergone 180° MLT at minimum follow-up of 6 months. Although no complications were noted and the procedure was well tolerated, only 2.5 % of eyes had greater than 20 % decrease in IOP and 7.5 % had 3 mmHg or more decrease in IOP [43].

32.8.2 Titanium Sapphire Laser Trabeculoplasty

Another new modality in LTP is the Titanium Sapphire laser using the SOLX 790 laser (Occulogix, Ontario, Canada). The sapphire laser trabeculoplasty consists of a very short pulse duration and shorter wavelength that penetrates deep into the trabecular meshwork. Currently in phase III clinical trials, the efficacy of Titanium Sapphire laser trabeculoplasty (TLT) is being compared to ALT in patients having primary OAG with poorly controlled IOP on maximum tolerated medical therapy or prior failed glaucoma surgery. TLT emits flashlamp-pumped, near-infrared energy (790 nm) in pulses lasting 5–10 μs (duration between ALT and SLT). TLT has been shown to provide deeper tissue penetration than the other lasers currently in use for LTP without causing damage to the trabecular meshwork and may therefore be repeatable. TLT results in a significant "opening" of the trabecular meshwork with statistically significant decrease in IOP (20–30 %) and minimal complications [23]. A study compared patients with POAG who had been treated with TLT vs. ALT. At 15 months follow-up the study determined that both treatment modalities had similar IOP lowering capabilities with 32 % for TLT vs. 25 % in ALT [44]. Interestingly, the 790 nm laser has the ability to ablate gold, and is being researched as a modality to adjust the IOP lowering capability of the SOLX Gold Shunt in vivo after implantation (see Chap. 39).

Summary for the Clinician

- Newer laser platforms are being studied for LTP, and include MLT and TLT.
- Other than small case series, there is no published data on trials with these newer lasers at the time of this publication.

References

1. The Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT) and glaucoma laser trial follow-up study, seven-year results. Am J Ophthalmol. 1995;120:718–31.
2. The Glaucoma Laser Trial Research Group. The Glaucoma Laser Trial (GLT). Results of argon laser trabeculoplasty versus topical medicines. Ophthalmology. 1990;97:1403–13.
3. Kramer TR, Noecker RJ. Comparison of the morphologic changes after selective laser trabeculoplasty and argon laser trabeculoplasty in human eye bank eyes. Ophthalmology. 2001;108:773–9.
4. Rodrigues MM, Spaeth GL, Donohoo P. Electron microscopy of argon laser therapy in phakic open-angle glaucoma. Ophthalmology. 1982;89:198–210.
5. Latina MA, Park C. Selective targeting of trabecular meshwork cells: in vitro studies of pulsed and CW laser interactions. Exp Eye Res. 1995;60:359–71.
6. Barkana Y, Belkin M. Selective laser trabeculoplasty. Surv Ophthalmol. 2007;52:634–54.
7. Damji KF, Shah KC, Rock WJ, et al. Selective laser trabeculoplasty vs. argon laser trabeculoplasty: a prospective randomized clinical trial. Br J Ophthalmol. 1999;83(6):718–22.
8. Damji KF, Bovell AM, Hodge WG, et al. Selective laser trabeculoplasty versus argon laser trabeculoplasty: results from a 1-year randomized clinical trial. Br J Ophthalmol. 2006;90:1490–4.
9. Juzych MS, Chopra V, Banitt MR, et al. Comparison of long-term outcomes of selective laser trabeculoplasty versus argon laser trabeculoplasty in open angle glaucoma. Ophthalmology. 2004;111:1853–9.
10. Latina MA, Sibayan SA, Shin DH, et al. Q-switched 532 nm Nd:YAG laser trabeculoplasty (selective laser trabeculoplasty): a multi-center, pilot, clinical study. Ophthalmology. 1998;105:2082–90.
11. Nagar M, Ogunyomade A, O'Brart DP, et al. A randomized, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. Br J Ophthalmol. 2005;89:1413–7.
12. Melamed S, Simon B, Levkovitz-Verbin H. Selective laser trabeculoplasty as primary treatment for open-angle glaucoma: a prospective, non-randomized pilot study. Arch Ophthalmol. 2003;121:957–60.
13. McIlraith I, Strasfeld M, Colev G, et al. Selective laser trabeculoplasty as initial and adjunctive treatment for open angle glaucoma. J Glaucoma. 2006;15: 124–30.
14. Katz L, Steinmann WC, Kabir A, Milineaux J, Wizov SS, Marcellino G, SLT/Med Study Group. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: a prospective, randomized trial. J Glaucoma. 2012;21(7):460–8.
15. Francis BA, Ianchulev T, Schofield JK, Minckler DS. Selective laser trabeculoplasty as a replacement for medical therapy in open angle glaucoma. Am J Ophthalmol. 2005;140(3):524–5.
16. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and adherence with topical glaucoma therapy. Am J Ophthalmol. 2005;140:598–606.
17. Kass MA, Meltzer DW, Gordon M, Cooper D, Goldberg J. Compliance with topical pilocarpine treatment. Am J Ophthalmol. 1986;101:515–23.
18. Greenidge KC, Spaeth GL, Fiol-Silva Z. Effect of argon laser trabeculoplasty on the glaucomatous diurnal curve. Ophthalmology. 1983;90:800–4.
19. Lee AC, Mosaed S, Weinreb RN, Kripke DF, Liu JH. Effect of laser trabeculoplasty on nocturnal intraocular pressure in medically treated glaucoma patients. Ophthalmology. 2007;114:666–70.
20. Nagar M, Luhishi E, Shah N. Intraocular pressure control and fluctuation: the effect of treatment with selective laser trabeculoplasty. Br J Ophthalmol. 2009;93(4):497–501.
21. Prasad N, Murthy S, Dagianis JJ, Latina MA. A comparison of the intervisit intraocular pressure fluctuation after 180 and 360 degrees if selective laser trabeculoplasty (SLT) as primary therapy in primary open angle glaucoma and ocular hypertension. J Glaucoma. 2009;18(2):157–60.
22. Klamann MK, Maier AK, Gonnermann J, Ruokonen PC. Adverse effects and short term results after selective laser trabeculoplasty. J Glaucoma. 2014; 23(2):105–8.
23. Knickelbein JE, Singh A, Flowers BE, Nair UK, et al. Acute corneal edema with subsequent thinning and hyperopic shift following selective laser trabeculoplasty. J Cataract Refract Surg. 2014;40(10): 1731–5.
24. Ozkok A, Tamcelik N, Ucar Comlekoglu D, Iskeleli G. Corneal decompensation after selective laser trabeculoplasty. Case Rep Ophthalmol Med. 2014;2014: 851971.
25. Tardif A, Bonnin N, Borel A, et al. Selective laser trabeculoplasty: results after a first and second session, overall comparison and results for three indications. J Fr Ophthalmol. 2014;37:353–7.
26. Hong BK, Winer JC, Martone JF, Wand M, Altman B, Shields B. Repeat selective laser trabeculoplasty. J Glaucoma. 2009;18:180–3.
27. Buys YM. Economics of selective laser trabeculoplasty as primary therapy for glaucoma. Can J Ophthalmol. 2006;41:419–20.
28. Lee R, Hutnik CM. Projected cost comparison of selective laser trabeculoplasty versus glaucoma medication in the Ontario Health Insurance Plan. Can J Ophthalmol. 2006;41:449–56.
29. Simon G, Lowery JA. Comparison of three types of lasers in laser trabeculoplasty in human donor eyes and clinical study. Abstract presented at 2007 ASCRS Symposium, San Diego.
30. Grayson DK, Camras CB, Podos SM, Lustgarten JS. Long-term reduction of intraocular pressure after repeat argon laser trabeculoplasty. Am J Ophthalmol. 1988;106:312–21.
31. Richter CU, Shingleton BJ, Bellows AR, et al. Retreatment with argon laser trabeculoplasty. Ophthalmology. 1987;94:1085–9.

32. Feldman RM, Katz LJ, Spaeth GL, et al. Long-term efficacy of repeat argon laser trabeculoplasty. Ophthalmology. 1991;98:1061–5.
33. Ha JH, Bowling B, Chen SD. Cystoid macular edema following selective laser trabeculoplasty in a diabetic patient. Clin Experiment Ophthalmol. 2014;42(2):200–1.
34. Melamed S, Pei J, Epstein DL. Short term effect of argon laser trabeculoplasty in monkeys. Arch Ophthalmol. 1985;103:1546–52.
35. Bradley JM, Anderssohn AM, Colvis CM, et al. Mediation of laser trabeculoplasty-induced matrix metalloproteinase expression by IL-1 beta and TNF-alpha. Invest Ophthalmol Vis Sci. 2000;41:422–30.
36. Alvarado JA, Alvarado RG, Yeh RF, Franse-Carman L, Marcellino GR, Brownstein MJ. A new insight into the cellular regulation of aqueous outflow: how trabecular meshwork endothelial cells drive a mechanism that regulates the permeability of Schlemm's canal endothelial cells. Br J Ophthalmol. 2005;89:1500–5.
37. Bylsma SS, Samples JR, Acott TS, Van Buskirk EM. Trabecular cell division after argon laser trabeculoplasty. Arch Ophthalmol. 1988;106:544–7.
38. Acott TS, Samples JR, Bradley JM, et al. Trabecular repopulation by anterior trabecular meshwork cells after laser trabeculoplasty. Am J Ophthalmol. 1989;107:1–6.
39. Bylsma SS, Samples JR, Acott TS, et al. DNA replication in the cat trabecular meshwork after argon laser trabeculoplasty in vivo. J Glaucoma. 1994; 3:36–43.
40. Dueker DK, Norberg M, Johnson DH, et al. Stimulation of cell division by argon and Nd:YAG laser trabeculoplasty in cynomolgus monkeys. Invest Ophthalmol Vis Sci. 1990;31:115–24.
41. Fea AM, Bosone A, Rolle T, Brogliatti B, Grignolo FM. Micropulse diode laser trabeculoplasty (MDLT): a phase II clinical study with 12 months follow-up. Clin Ophthalmol. 2008;2(2):247–52.
42. Detry-Morel M, Muschart F, Pourjavan S. Micropulse diode laser (810 nm) vs. argon laser trabeculoplasty in the treatment of open angle glaucoma: comparative short term safety and efficacy profile. Bull Soc Belge Ophthalmol. 2008;308:21–8.
43. Rantala E, Valimaki J. Micropulse laser diode trabeculoplasty—180 degree treatment. Acta Ophthalmol. 2012;90:441–4.
44. Goldenfeld M, Melamed S, Simon G, Ben Simon GJ. Titanium: sapphire laser trabeculoplasty versus argon laser trabeculoplasty in patients with open-angle glaucoma. Ophthalmic Surg Lasers Imaging. 2009;3:264–9.

Procedural Treatments: Endoscopic Cyclophotocoagulation

33

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Core Messages

- Endoscopic cyclophotocoagulation (ECP) has been used to treat a variety of glaucoma diagnoses that have been refractory to medical and surgical therapy, and can be used in eyes with good potential vision and moderately elevated intraocular pressure (IOP).
- ECP is currently investigated and used as a primary glaucoma surgery; however, caution should be taken in such situations.
- Compared with transscleral cyclophotocoagulation, ECP is less likely to cause excessive trauma to the ciliary processes or adjacent structures.
- ECP can be performed through a limbal or pars plana approach; the limbal approach is recommended if it can be performed effectively and safely.
- Postoperatively, glaucoma medications should be continued and usually the patient will need to remain on one or more medications for the long term.
- Reported complications of ECP include fibrin exudates, hyphema, cystoid macular edema, vision loss, choroidal detachment, retinal detachment, hypotony, and phthisis.
- The IOP can usually be expected to drop starting about 1–2 weeks after the surgery.

33.1 When Can or Should Endoscopic Cyclophotocoagulation Be Used?

The indication for performing ECP is glaucoma that has been refractory to medical and/or filtering surgery [1–9]. Many types of glaucoma have been treated with ECP, including primary open-angle, pseudo-exfoliation, neovascular, pediatric, and angle-closure. In a prospective comparative Brazilian study of ECP vs. Ahmed valve in 68 patients with IOP greater than 35 mmHg on maximally tolerated medications, ECP was found to be an effective surgery for various forms of glaucoma with fewer complications. After 24 months follow-up, the probability of success and mean IOP was approximately equal between the two groups. The tube shunt group experienced more choroidal detachments and shallow anterior chambers, while the number of hyphemas was almost equal between groups. More eyes in the

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ECP group experienced significant inflammation. ECP has also been used in conjunction with cataract extraction as a primary glaucoma surgery [2–4, 10]. However, I do not typically use ECP as a primary glaucoma surgery, either alone or in conjunction with cataract extraction.

As opposed to transscleral cyclophotocoagulation (TCP), which is traditionally reserved for eyes with low vision potential, eyes with relatively intact central visual acuity are appropriate candidates for ECP [2–5, 10]. However, since the IOP-lowering effect of ECP is usually modest, in eyes with very elevated pressures or with advanced glaucoma that require very low IOP filtration surgeries are still the procedures of choice. ECP is difficult to perform in phakic eyes because of the probe size, and there is significant risk of lens damage. For inexperienced ECP users in whom maintaining phakia is a goal, ECP should not be performed.

Summary for the Clinician

- ECP can be used for a variety of glaucoma diagnoses: open-angle, narrow-angle, aphakic/pseudophakic, pediatric, neovascular.
- ECP can be used on eyes with good vision potential.
- Some clinicians use ECP as a primary glaucoma procedure, especially combined with phacoemulsification; however, controversy exists over this practice.
- A phakic eye is a contraindication (relative) to ECP.

33.2 Should ECP Be Used as a Primary Surgery for Glaucoma?

ECP is increasingly being used as a primary surgery for the treatment of glaucoma. A recent multicenter study supported by the laser's manufacturer, Endo Optiks, Inc., has shown a reduced need for glaucoma medications after combined ECP and phacoemulsification cataract extraction as compared with cataract surgery only [10]. However, caution is warranted in the use of cyclodestruction as a first-line surgical therapy. There are some significant concerns with the indiscriminant use of ECP in all glaucoma patients who are undergoing cataract extraction. ECP has the potential for serious adverse events, including cystoid macular edema (CME), retinal detachment, hypotony (due to theoretical hyposecretion of aqueous), and phthisis bulbi [3, 5]. Furthermore, there is a significant learning curve to the procedure and inexperienced surgeons may encounter intraoperative complications more frequently compared with those who have become facile with the procedure. Finally, the long-term efficacy of glaucoma procedures is usually measured on the order of 5 years; such long-term data on the results of ECP remain to be seen.

Summary for the Clinician

- Long-term data do not yet exist on the outcomes of ECP.
- Caution is advised in the use of ECP as a primary surgery, given its potential for serious complications.

33.3 Is Burning the Ciliary Processes a Safe Thing to Do?

Hypotony due to destruction of the ciliary processes that produce aqueous humor is a theoretical concern with this procedure. Again, it must be emphasized that there are no published randomized controlled trials on this topic and no long-term data on adults. The longest published follow-up is in aphakic/pseudophakic children (mean follow-up 44 months) and it showed no hypotony [9]. Another report in children with Peter's anomaly did report cases of chronic hypotony [11].

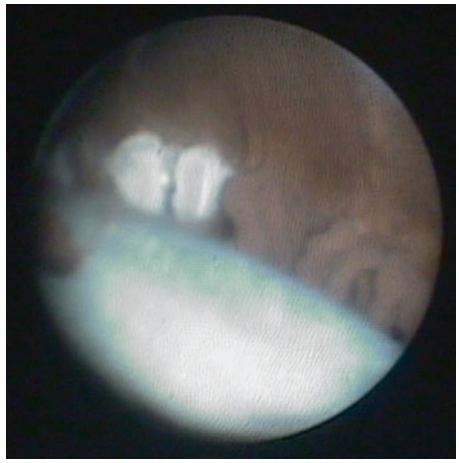

Fig. 33.1 Endoscopic view during endoscopic photocoagulation treatment. Note the whitened ciliary processes on the left side that have been treated and the brown untreated processes on the right

The question asked above has to be answered relative to other treatments available. Medical therapy is probably safer than ciliary destruction. Unwanted side effects of medical therapy are generally reversible with discontinuation of the offending agent. Compared to TCP, which also "burns" the ciliary processes, but from an external approach, ECP appears to be a relatively safe procedure. TCP often causes excessive damage to the ciliary processes and adjacent tissues, such as the iris root and pars plana [12–14]. By contrast, with ECP coagulation of the ciliary processes is directly visualized so that energy can be titrated during the procedure to avoid overtreatment and excessive damage to adjacent tissues (Fig. 33.1).

Summary for the Clinician

- As compared to TCP, ECP is a more targeted procedure and less likely to cause excessive damage to adjacent tissues.
- Chronic hypotony due to hyposecretion of aqueous humor is a concern with ECP; however, at this time we cannot identify who is at greater risk for this possible complication.

33.4 Technically, How Is ECP Performed?

The ECP laser device (E2, Endo Optiks, Inc., Little Silver, NJ) incorporates a diode laser that emits pulsed continuous-wave energy at 810 nm, a 175 W xenon light source, a helium–neon laser aiming beam, and video camera imaging system that can be recorded (Fig. 33.2). ECP can be done through the limbus or pars plana. For either approach, a retrobulbar block with lidocaine and bupivacaine is recommended, or general anesthesia can be considered in selective cases. The limbal approach is preferred to the pars plana approach because it avoids anterior vitrectomy and its associated risks of choroidal and retinal detachment. However, there are cases that are more safely approached through the pars plana, for example, in aphakic eyes with posterior synechia limiting access to the ciliary sulcus.

In the limbal approach, the pupil is pharmacologically dilated. I create a paracentesis port and fill the anterior chamber with viscoelastic agent, which is then further used to expand the nasal posterior sulcus. The sulcus must be opened up to allow the ECP probe easier access to the pars plicata. One wants to avoid hitting the iris with the probe or burning it with the probe's energy to minimize postoperative inflammation. A 2.2 mm keratome is then used to enter into the anterior chamber at the temporal limbus. After orientation of the probe image outside of the eye, the 18- or 20-gauge probe is inserted through the incision and into the posterior sulcus. At this time, the ciliary processes are viewed on the monitor and treatment can begin. The laser is set on continuous wave and energy settings are 30–90 mW. A 180° span of ciliary processes is photocoagulated (more area can be treated if a curved probe is used). Laser energy is applied to each process until shrinkage and whitening occur (Fig. 33.1). The probe should be held far away enough so that 3–4 processes can be viewed at once. When the probe is located closer to the process, the energy delivered per unit area increases. Ciliary processes are treated individually or in a "painting" fashion across multiple processes. If excessive

Fig. 33.2 The endoscopic cyclophotocoagulation device incorporates a laser unit and video monitor for viewing the ciliary processes during treatment

energy is used, the process explodes (or "pops") with bubble formation, leading to excessive inflammation and breakdown of the blood–aqueous barrier. After the nasal 180° of ciliary processes are treated, a separate incision is created at the nasal limbus in a similar fashion as above. The temporal processes are then photocoagulated for a total of up to 360°, if so desired. I typically treat approximately 270–360°. Prior to closure of the wounds, viscoelastic is removed from the anterior chamber with irrigation and aspiration. Wounds are then closed with single interrupted 10-0 nylon sutures.

In the pars plana approach, an infusion port is inserted through the inferior pars plana and two superior entries are created for vitrectomy and illumination. Only a limited anterior vitrectomy is performed to allow adequate and safe access to all of the ciliary processes. The ECP probe can be inserted through each superior entry for treatment of the opposite 180° of processes. There may be a few superior processes that cannot be accessed as the entry ports are not exactly 180° opposite each other. Laser cyclophotocoagulation is carried out with the same parameters and endpoints as described for the limbal approach. If the anterior segment surgeon has not had extensive experience in posterior segment surgery, assistance from a retinal surgeon should be sought for the establishment of the pars plana entry ports and the limited anterior vitrectomy. Risk of inadvertent choroidal and/or retinal detachment is a serious concern and should be minimized. The pars plana approach should not be used in a phakic patient since injury to the lens is likely.

In all patients, whether under local or general anesthesia, retrobulbar bupivicaine is administered before or at the end of surgery to minimize postoperative pain. Sub-Tenon's injection of 1 cm^3 of triamcinolone (40 mg/cm^3) and/or subconjunctival steroid is also given for inflammation and the prevention of CME.

Summary for the Clinician

- ECP can be performed via a limbal or pars plana approach.
- The limbal approach is usually recommended for anterior segment surgeons; incisions for the probe can be made with a 2.2 mm microkeratome.
- Treatment of the ciliary processes, until whitening and shrinkage is seen, is performed over 270–360° so as to achieve adequate IOP control.
- If popping or ciliary process explosions are seen, the probe should be moved further away from the process or energy should be decreased on the laser.
- Do not use the pars plana approach in phakic patients.
- Local injections of anesthetic should be given for pain control and sub-Tenons or subconjunctival steroid can be given for expected inflammation.

33.5 How Is the Postoperative Course of ECP Managed?

On postoperative day 1, patients are placed on a regimen of topical antibiotics, steroids, nonsteroidal antiinflammatory agents (NSAIDs), and cycloplegics. They should continue their preoperative glaucoma medications, except for miotics and prostaglandin analogs (if IOP is not very high) since these may exacerbate intraocular inflammation or its sequelae. The frequency of topical steroids is tailored to the degree of inflammation. Antibiotics are discontinued after 1 week, and the steroids, NSAIDs, and cycloplegics are tapered as inflammation subsides. IOP-lowering medications are removed according to the IOP targets. Administration of acetazolamide during the evening of surgery may be used to prevent a spike in IOP from underlying glaucoma, inflammation, or possible retained viscoelastic.

Summary for the Clinician

- The postoperative regimen includes topical antibiotics, steroids, NSAIDs, cycloplegics, and the preoperative glaucoma medications, excluding miotics and prostaglandins if the IOP is in a safe range.
- Oral carbonic anhydrase inhibitors should be considered during the evening of surgery.

33.6 What Are Complications that May Be Encountered and How Are They Specifically Managed?

In the largest series to date, complications associated with ECP included fibrin exudate in 24 %, hyphema in 12 %, CME in 10 %, vision loss of two lines or greater in 6 %, and choroidal detachment in 4 % [3]. Other publications have reported serious complications including retinal detachment, hypotony, and phthisis [5, 7, 9]. Although not reported in the literature, endophthalmitis and choroidal hemorrhage are potential complications as well, due to the intraocular nature of the surgery.

Inflammation and fibrin exudates can be observed frequently and should be treated with aggressive topical steroid therapy. In most cases, the fibrin will resolve without additional treatment. However, if the fibrin is persistent or substantial, causing severe and/or prolonged visual impairment, intracameral tissue plasminogen activator (TPA) (0.1 mL containing 25 mcg) can be utilized for rapid resolution. Cases of hyphema can also be observed and treated conservatively with topical steroids and cycloplegics. Recurrence is uncommon. Postoperative IOP elevation should be managed with appropriate topical and systemic glaucoma medications. CME may be treated with topical steroids and NSAIDs. Posterior sub-Tenons or intravitreal steroids are options if the topical regimen is inadequate. Choroidal detachments usually resolve with time. Topical steroids and cycloplegics

can help expedite resolution. Persistent hypotony is more problematic if the cause is long-term aqueous shutdown from the ECP. Glaucoma therapy should be discontinued, including oral medications if this is safe for the contralateral eye. Topical cycloplegics and steroids may help treat ciliochoroidal detachment if this is a component of the hypotony.

Summary for the Clinician

- A variety of complications can occur with ECP, including serious events such as retinal detachment and hypotony.
- In many cases, conservative treatment with steroids, NSAIDs, and cycloplegics can be effective in resolving the complication.

33.7 When Can I Expect the Pressure Drop to Occur?

Patients should continue preoperative glaucoma medications initially following surgery. Prostaglandin analogs and Pilocarpine, which can exacerbate inflammation, may be withheld if the IOP is in an acceptable range. Typically, the pressure drop is observed at 1–2 weeks after ECP. Glaucoma medications can be gradually tapered as the IOP allows. In most cases medications cannot be completely tapered. In the paper by Chen et al. [3], the mean number of medications dropped from three preoperatively to two postoperatively, with a follow-up of 12.9 months.

Summary for the Clinician

- The IOP usually begins to drop 1–2 weeks after surgery and medications can be tapered accordingly.

33.8 What Is the Long-Term Safety Data on This Procedure?

There is a paucity of peer-reviewed long-term data on ECP. The mean follow-up periods for the Chen et al. [3] and Lima et al. [5] studies were 12.9 and 21.3 months, respectively. A couple recent papers have reported the safety and efficacy of ECP combined with phacoemulsification for up to 24 months [15, 16]. Complications (including short-term) included steroid-related IOP elevation, vitreous in the anterior chamber, anterior uveitis, hyphema, and CME. Longer term follow-up data (mean of 44 months) have been reported for pediatric cases of aphakic/pseudophakic glaucoma [9].

For the long term, the primary safety concern is elevation of IOP and need for further treatment. In the pediatric series by Carter et al., the success rate was 53 % after a mean follow-up of 44 months [9]. The major complications were two retinal detachments, which occurred within a month of surgery. No cases of hypotony occurred.

Summary for the Clinician

- There is minimal published long-term data on ECP.

References

1. Uram M. Ophthalmic laser microendoscope ciliary process ablation in the management of neovascular glaucoma. Ophthalmology. 1992;99:1823–8.
2. Uram M. Combined phacoemulsification, endoscopic ciliary process photocoagulation, and intraocular lens implantation in glaucoma management. Ophthalmic Surg. 1995;26:346–52.
3. Chen J, Cohn RA, Lin SC, et al. Endoscopic photocoagulation of the ciliary body for treatment of refractory glaucomas. Am J Ophthalmol. 1997;124(6):787–96.
4. Gayton JL, Van De Karr M, Sanders V. Combined cataract and glaucoma surgery: trabeculectomy versus endoscopic laser cycloablation. J Cataract Refract Surg. 1999;25:1214–9.

5. Lima FE, Magacho L, Carvalho DM, Susanna Jr R, Avila MP. A prospective, comparative study between endoscopic cyclophotocoagulation and the Ahmed drainage implant in refractory glaucoma. J Glaucoma. 2004;13(3):233–7.
6. Neely DE, Plager DA. Endocyclophotocoagulation for management of difficult pediatric glaucomas. J AAPOS. 2001;5:221–9.
7. Plager DA, Neely DE. Intermediate-term results of endoscopic diode laser cyclophotocoagulation for pediatric glaucoma. J AAPOS. 1999;3(3):131–7.
8. Al-Haddad CE, Freedman SF. Endoscopic laser cyclophotocoagulation in pediatric glaucoma with corneal opacities. J AAPOS. 2007;11(1):23–8.
9. Carter BC, Plager DA, Neely DE, Sprunger DT, Sondhi N, Roberts GJ. Endoscopic diode laser cyclophotocoagulation in the management of aphakic and pseudophakic glaucoma in children. J AAPOS. 2007;11(1):34–40.
10. Berke SJ, Sturm RT, Caronia RM, Nelson DB, D'Aversa G, Freedman M. Phacoemulsification combined with endoscopic cyclophotocoagulation (ECP) in the management of cataract and medically controlled glaucoma: A large, long term study. Paper presented at the American Glaucoma Society meeting, Charleston, Abstract. 2006;22:47.
11. Al-Haddad CE, Freedman SF. Endoscopic laser cyclophotocoagulation in pediatric glaucoma with corneal opacities. J AAPOS. 2007;11:23–8.
12. McKelvie PA, Walland MJ. Pathology of cyclodiode laser: a series of nine enucleated eyes. Br J Ophthalmol. 2002;86(4):381–6.
13. Schubert HD, Agarwala A. Noncontact and contact pars plana transscleral neodymium: YAG laser cyclophotocoagulation in postmortem eyes. Ophthalmology. 1989;96(10):1471–5.
14. Schuman JS, Noecker RJ, Puliafito CA, Jacobson JJ, Shepps GJ, Wang N. Energy levels and probe placement in contact transscleral semiconductor diode laser cyclophotocoagulation in human cadaver eyes. Arch Ophthalmol. 1991;109(11):1534–8.
15. Francis BA, Berke SJ, Dustin L, Noecker R. Endoscopic cyclophotocoagulation combined with phacoemulsification versus phacoemulsification alone in medically controlled glaucoma. J Cataract Refract Surg. 2014;40(8):1313–21. doi:10.1016/j.jcrs.2014.06.021.
16. Lindfield D, Ritchie RW, Griffiths MF. 'Phaco-ECP': combined endoscopic cyclophotocoagulation and cataract surgery to augment medical control of glaucoma. BMJ Open. 2012;2(3):Pii. doi:10.1136/bmjopen-2011-000578.

34 Procedural Treatments: Transscleral Cyclophotocoagulation

Hylton R. Mayer, James C. Tsai, and M. Bruce Shields

Core Messages

- Transscleral cyclophotocoagulation (TCP) is a useful tool for glaucoma management.
- TCP is typically reserved for those patients with limited visual potential and who are at high risk of failure with other treatment approaches.
- Most complications of TCP are mild and easily managed, but one should be aware of the low but real risk of serious complications such as phthisis and sympathetic ophthalmia.
- Patient education and careful follow-up are often the best way to avoid medicolegal problems with eyes that are severely compromised at baseline.

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34.1 What Is Transscleral Cyclophotocoagulation?

In the last few decades, cyclodestructive procedures, such as diathermy, cryotherapy, therapeutic ultrasound, β-irradiation, and electrolysis, have been employed in the management of recalcitrant glaucomas. Currently, the standard method of therapeutic cyclodestruction is cyclophotocoagulation, using a light source. The practicality, efficacy, and well-established clinical record of TCP make it a useful tool for refractory glaucoma management (Fig. 34.1) [1].

Transscleral cyclodestruction by light energy was developed by Weekers in 1961 [2]. The original xenon-arc lamps and ruby lasers have been replaced by commercially available neodymium:YAG and semiconductor diode lasers, with transscleral diode cyclophotocoagulation currently the most commonly used cyclodestructive procedure. The target tissue and mechanism of action have remained essentially unchanged for all forms of cyclophotocoagulation, which is widely believed to lower intraocular pressure (IOP) by disrupting the pars plicata of the ciliary body, subsequently decreasing aqueous production (Fig. 34.2) [3, 4]. Some studies have suggested that cyclophotocoagulation also lowers IOP by causing an increase in outflow through the uveoscleral pathways [5, 6].

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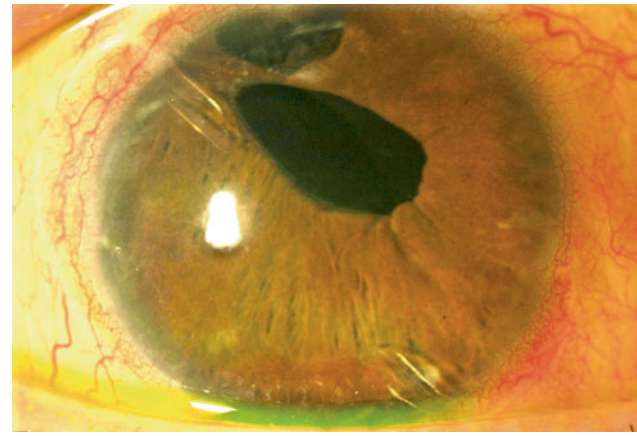

Fig. 34.1 An eye with aphakic glaucoma that has undergone multiple incisional surgeries (Courtesy of The Yale Eye Center)

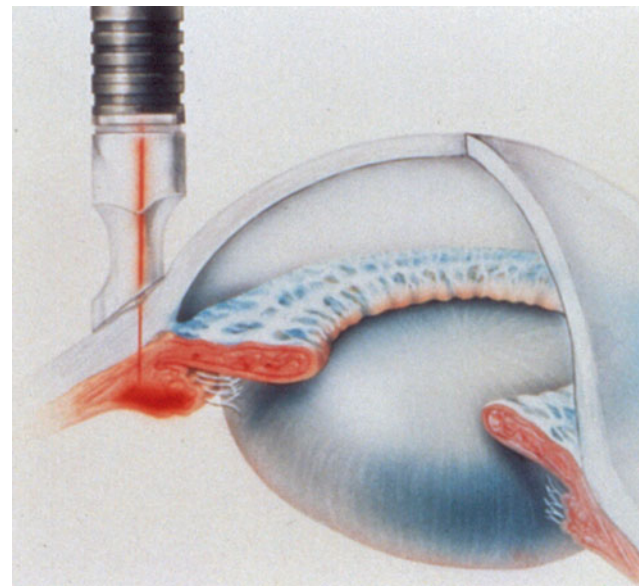

Fig. 34.2 Schematic demonstrating transscleral cyclophotocoagulation using a diode laser and G-Probe (Image provided by IRIDEX)

Summary for the Clinician

- Transscleral cyclophotocoagulation is a laser treatment directed at the pars plicata, which decreases aqueous production.

34.2 When Should I Use TCP? Should It Be Used as a Primary Surgery for Glaucoma?

While some studies have reported success with TCP as a primary procedure, we typically reserve TCP for those patients with limited visual

potential who are at high risk of failure with other treatment approaches [7, 8]. Even in this population, however, the risk–benefit ratio often favors medical management initially in an effort to achieve safe IOP reduction. Prior to consideration of TCP, most patients will be tried on maximum topical therapy and possibly even oral carbonic anhydrase inhibitors.

TCP is most often utilized in patients with significantly limited vision, although the cut-off level of vision varies depending on individual patient circumstances. Patients with 20/400 to hand motion (HM) vision with multiple failures of previous incisional surgical interventions, or those with significant social or physical impediments to incisional surgery intervention, might be considered reasonable TCP candidates. Patients with no light perception (NLP) typically require TCP intervention only if they are having intractable pain.

Many candidates for TCP have had one or more failures of previous surgical interventions. Glaucomatous disorders with a high risk for failure of filtering surgery include neovascular, uveitic, epithelial ingrowth, as well as any glaucomatous process with significantly scarred conjunctive from prior glaucoma or other ocular surgery [9–11].

Pediatric glaucomas represent a unique spectrum of glaucomatous disorders that may benefit from earlier consideration of TCP. When trabeculectomy or goniotomy is not effective or not indicated, TCP may be a reasonable alternative intervention, considering the often unfavorable course of filtering surgery or glaucoma drainage devices in this population [12–18]. Pediatric patients receiving TCP achieve IOP control 40–70 % of the time after one treatment, but most pediatric patients require multiple TCP treatments to maintain IOPs below 21 mmHg [19–22]. TCP use in children is also associated with a lower incidence of vision loss and fewer severe complications compared to adults who receive TCP [17–20].

Summary for the Clinician

- TCP is typically reserved for those patients with limited visual potential and who are at high risk of failure with other treatment approaches.
- TCP has been shown to be relatively safe and effective in pediatric glaucoma.

34.3 Technically, How Is TCP Performed?

A tremendous benefit of TCP, especially with the portable diode unit, is that it can be safely and easily performed in a clinical setting, such as the examination room or even a hospital room. Most patients who are able to tolerate peribulbar or retrobulbar anesthesia without sedation are suitable candidates for clinic-based TCP. Possible complications related to orbital anesthesia include retrobulbar hemorrhages, vasovagal responses, or central nervous system depression [23–28]. Support systems should be available for the management of these rare but vision- or life-threatening complications.

We prefer clinic-based TCP in most cases, because of the convenience and decreased financial burden to the patient. We have found that the orbital anesthesia and laser procedure can be safely executed and well tolerated in the vast majority of cases. In some situations, patient comfort and safety may be improved in a controlled operating room setting, and surgeons should practice according to their level of comfort and the standard of care within their medical community.

A retrobulbar block of 4–6 mL of a 50:50 mixture of 2 % lidocaine and 0.75 % bupivacaine is administered using an Atkinson needle. Manual pressure is held on the eye for 1–2 min after the block to reduce the chance for retrobulbar hemorrhage. After approximately 10 min, the

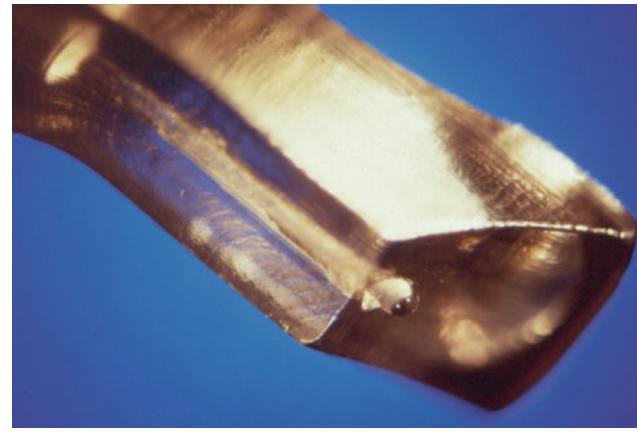

Fig. 34.3 Close-up photograph of the G-Probe footplate (Image provided by IRIDEX)

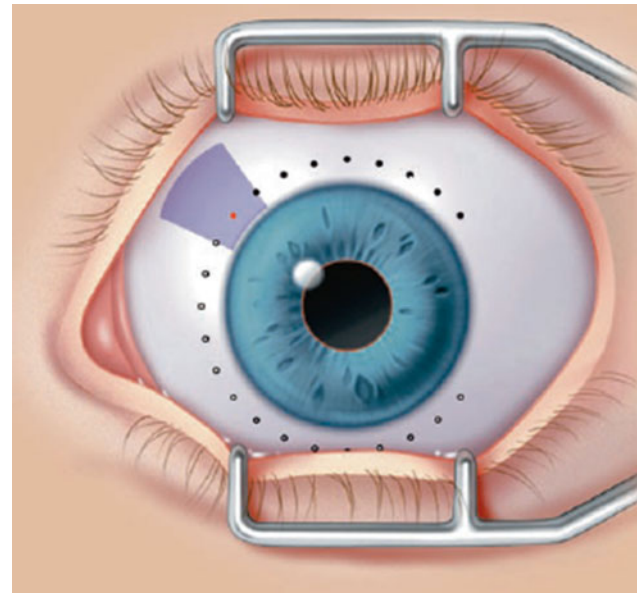

Fig. 34.4 Drawing illustrating the ideal placement and spacing of the G-Probe footplate (Image provided by IRIDEX)

cornea and conjunctiva are checked for sensation and the block is repeated if necessary.

We use the IRIS Oculight SLx Diode Laser with G-Probe (Iris Medical Inc. Mountain View, CA) semiconductor diode laser, which is portable, solid-state, and requires no special electrical outlet or water for cooling (Fig. 34.3). Our initial settings are 1750–2000 mW for 2000 ms. We will occasionally transilluminate the eye with a Fenhoff muscle light to identify the ciliary body, especially when the anatomy is distorted. In most cases, however, the G-probe is designed to provide adequate placement, in such a way that positioning the anterior edge of the footplate on the limbus directs the laser energy 1.2 mm posterior to the limbus, corresponding to the pars plicata of the ciliary body. We usually initiate treatment at the 12 o'clock position and listen for a delayed popping sound, which indicates excessive tissue disruption. If the sound is heard at the initial setting, the power is reduced by 250 mW increments until the sound is no longer heard. Conversely, if after the first laser application no popping sound is heard, we increase the power by 250 mW increments until a pop is heard and then decrease it by 250 mW. In either case, we move clockwise for each subsequent application. Applications are spaced by placing the side of the footplate adjacent to the indentation of the fiberoptic made by the prior application (Fig. 34.4). Once the desired

power is established, the treatments are continued for a total of 21–24 applications over 360°. An earlier protocol called for 18 applications over 270°, but we found that this requires too many repeat procedures and feel that better results are achieved with the 360° treatment. Occasionally a late popping sound is not heard despite maximum power of 3000 mW. In these instances, if the fiber optic probe has been used repeatedly, it may need to be replaced. Otherwise, we will proceed with treatment at 3000 mW and often repeat the first five clock hours that had presumably been undertreated. We avoid laser applications over thin blebs or glaucoma drainage device tubes. Some surgeons advocate avoiding the 3 and 9 o'clock positions to minimize the risk to the long posterior ciliary arteries, but this is not necessary, since the two arteries branch widely well posterior to the site of laser applications.

We reuse our G-probes approximately 5 times before replacing, or we may replace the probes sooner if there is evidence of fiber optic damage or decreasing performance. Numerous reports have documented the reliability of the G-probe's energy output after multiple uses [29, 30]. Before and after each use, we clean the probe with 70 % isopropyl alcohol and visually inspect the tip for abnormalities. Debris caught in the lumen can become charred, which can decrease the energy subsequently delivered. Others clean the tip with mild dish detergent followed by a water rinse and then a 20 min soak in hydrogen peroxide followed by another water rinse and drying. One paper reported no adverse effects to the probe appearance or performance after sterilization with ethylene oxide [31].

Summary for the Clinician

- TCP can be safely and easily performed in a clinical setting, such as the examination room or even a hospital room.
- A retrobulbar block is necessary.
- Treating 360° reduces the number of repeat procedures and has not been associated with increased phthisis in our patients.
- Initial power is set at 1750–2000 mW and is adjusted according to the auditory pop which indicates too much power, while 2000 ms is constant.
- The G-probe of the diode laser unit can be reused several times without sacrificing safety or efficacy.

34.4 How Should One Manage the Postoperative Course? When Can One Expect the Pressure to Drop After TCP? When Can Medications be Tapered off After TCP?

Upon completion of the procedure, a steroid or steroid–antibiotic ointment and 1 % atropine drops are applied to the eye, and the eye is patched overnight or at least until the anesthesia has worn off. The patient is seen the following day and started on prednisolone 1 % qid and occasionally continued on the atropine 1 % bid. Most patients continue with their IOP-lowering drops until the IOP-lowering effect of TCP is observed, although prostaglandin analogs and cholinergics are usually stopped after the procedure. The prednisolone and atropine are tapered off as the inflammation and discomfort improve, usually over the course of 1 month.

We expect to see a pressure-lowering effect by 1 week, although it can be appreciated as soon as 1 day. The maximum IOP-lowering effect is usually obtained by 1 month. IOP-lowering medications are tapered off gradually until safe IOPs are attained.

If IOPs are trending downward, we observe the patient until the pressures stabilize at a safe range. If pressures are consistently at an undesired level, we consider repeating the TCP. For persistently high IOPs, we have repeated TCP therapy as early as 1 week, but we prefer to delay retreatment for at least 1 month. Retreatments follow the same protocol as the initial treatment and typically involve 360°.

Summary for the Clinician

- Topical prednisolone 1 % qid and occasionally atropine 1 % bid are typically sufficient for inflammation management.
- IOP-lowering drops are decreased depending on the pressure-lowering response to TCP.
- One should expect to see a pressure-lowering effect by 1 week. IOP lowering may be appreciated as soon as 1 day, but it may take 1 month or more to see the full benefits.
- Retreatment, if necessary, is ideally delayed for 1 month, but can be performed as early as 1 week after the last TCP.
- Retreatment is performed over 360°.

34.5 What Complications May Be Encountered and How Can I Specifically Manage Each One? What Is the Long-Term Efficacy and Safety Data on TCP?

The patient will usually experience mild to moderate pain, which is often described as a dull headache, after the anesthesia wears off. However, the pain can typically be controlled by a mild analgesic, such as acetaminophen or ibuprofen, and is usually gone by the next morning.

Anterior chamber inflammation is expected after properly performed TCP, but it is usually controlled by prednisolone 1 % qid for approximately 10 days. Occasionally, patients will have severe inflammatory reactions, which usually can be controlled by increasing the frequency of prednisolone to every 1 or 2 h, although rarely a patient may require sub-Tenon's triamcinolone to control the inflammation. Many patients will manifest chronic aqueous flare after TCP, presumably due to a breakdown of the blood–aqueous barrier, but this chronic flare does not require medical intervention [32].

Subconjunctival hemorrhage and/or chemosis is not uncommon, but rarely significant. Intraocular hemorrhage is most commonly seen after TCP in patients with neovascular glaucoma. While bleeding can reduce vision and increase IOP, the hemorrhage is usually mild and transient, and requires no additional treatment measures. In patients with neovascular glaucoma, if time allows, intraocular anti-vascular endothelial growth factor (VEGF) agents and pan-retinal photocoagulation should be considered prior to TCP in an attempt to control pressure and reduce TCP-related hemorrhage. Ideally, TCP would be delayed 3–5 days after anti-VEGF therapy to allow for maximum regression of abnormal vascularization.

Antiglaucoma medications, with the exception of prostaglandin analogs and cholinergic agents, are continued postoperatively and gradually eliminated as the IOP decreases. Hypotony may occur after TCP and can be asymptomatic or visually significant. An appropriately concerning complication of TCP is hypotony leading to phthisis, which has been reported in up to 12 % of patients [1, 7, 8, 33–43]. Hypotony may be associated with a flat anterior chamber and choroidal detachments [44]. Cessation of IOP-lowering agents and control of inflammation are key factors to manage when treating post-TCP hypotony.

Vision loss has been reported to occur in approximately 40 % of patients who receive TCP [1, 7, 8, 33–43, 45]. In at least half of these cases, the vision loss can be attributed to the underlying ocular disorder that precipitated the glaucomatous process, while treatment-related vision loss may be related to hypotony, cystoid macular edema, or phototoxicity. Patients should be counseled appropriately during the consent process about the potential for vision loss.

Other rarely reported complications include cataract formation, retinal detachment, and sympathetic ophthalmia [11, 38, 46–49]. We rarely avoid TCP based on the risk of sympathetic ophthalmia, which we have never seen, but one should monitor the fellow eye carefully for this possibility. Patient education and careful follow-up are often the best way to avoid problems with eyes that are severely compromised at baseline.

TCP has been widely used to treat refractory glaucomas since its inception. Many treated eyes

have significant comorbidities and/or advanced glaucomatous optic neuropathy with limited visual potential, which can confound conclusions regarding safety and efficacy. There is also a lack of consensus and standardization regarding treatment success parameters. In general, TCP seems to achieve desired pressure reductions in reported ranges of 50–85 % [1, 7, 8, 31–41, 43, 50]. As one might expect, a higher percentage of patients with less comorbidity, such as traumatic glaucoma or aphakic glaucomas, maintain stable visual acuity, compared with patients with conditions such as neovascular or inflammatory glaucomas.

Summary for the Clinician

- Anterior chamber inflammation is expected and can usually be managed with topical steroids.
- Chronic flare after TCP is common and does not require treatment.
- If hypotony occurs, look for inflammation and discontinue IOP-lowering agents.
- Uncommon complications of TCP include retinal detachment, phthisis, or sympathetic ophthalmia. Infrequent complications are rarely reasons to avoid the procedure, but clinicians should be alert to their possible occurrence.
- Patient education and careful follow-up are often the best way to avoid medicolegal problems with eyes that are severely compromised at baseline.

References

1. Pastor SA, Singh K, Lee DA, et al. Cyclophotocoagulation: a report by the American Academy of Ophthalmology. Ophthalmology. 2001;108:2130–8.
2. Weekers R, Lavergne G, Watillon M, et al. Effects of photocoagulation of ciliary body upon ocular tension. Am J Ophthalmol. 1961;52:156.
3. Schubert HD, Federman JL. A comparison of CW Nd:YAG contact transscleral cyclophotocoagulation with cyclocryopexy. Invest Ophthalmol Vis Sci. 1989;30:536–42.
4. McKelvie PA, Walland MJ. Pathology of cyclodiode laser: a series of nine enucleated eyes. Br J Ophthalmol. 2002;86:381–6.
5. Schlote T, Beck J, Rohrbach JM, et al. Alteration of the vascular supply in the rabbit ciliary body by transscleral diode laser cyclophotocoagulation. Graefes Arch Clin Exp Ophthalmol. 2001;239:53–8.
6. Liu GJ, Mizukawa A, Okisaka S. Mechanism of intraocular pressure decrease after contact transscleral continuous-wave Nd:YAG laser cyclophotocoagulation. Ophthalmic Res. 1994;26:65–79.
7. Grueb M, Rohrbach JM, Bartz-Schmidt KU, et al. Transscleral diode laser cyclophotocoagulation as primary and secondary surgical treatment in primary open-angle and pseudoexfoliatve glaucoma. Long-term clinical outcomes. Graefes Arch Clin Exp Ophthalmol. 2006;244:1293–9.
8. Ansari E, Gandhewar J. Long-term efficacy and visual acuity following transscleral diode laser photocoagulation in cases of refractory and non-refractory glaucoma. Eye (Lond). 2007;21:936–40.
9. Tsai JC, Feuer WJ, Parrish 2nd RK, et al. 5-Fluorouracil filtering surgery and neovascular glaucoma. Long-term follow-up of the original pilot study. Ophthalmology. 1995;102:887–92.
10. Noble J, Derzko-Dzulynsky L, Rabinovitch T, et al. Outcome of trabeculectomy with intraoperative mitomycin C for uveitic glaucoma. Can J Ophthalmol. 2007;42:89–94.
11. Katz GJ, Higginbotham EJ, Lichter PR, et al. Mitomycin C versus 5-fluorouracil in high-risk glaucoma filtering surgery. Extended follow-up. Ophthalmology. 1995;102:1263–9.
12. Pakravan M, Homayoon N, Shahin Y, et al. Trabeculectomy with mitomycin C versus Ahmed glaucoma implant with mitomycin C for treatment of pediatric aphakic glaucoma. J Glaucoma. 2007;16:631–6.
13. al-Hazmi A, Zwaan J, Awad A, et al. Effectiveness and complications of mitomycin C use during pediatric glaucoma surgery. Ophthalmology. 1998;105:1915–20.
14. Sidoti PA, Belmonte SJ, Liebmann JM, et al. Trabeculectomy with mitomycin-C in the treatment of pediatric glaucomas. Ophthalmology. 2000;107:422–9.
15. Chaudry IA, Shamsi FA, Morales J. Orbital cellulitis following implantation of aqueous drainage devices. Eur J Ophthalmol. 2007;17:136–40.
16. van Overdam KA, de Faber JT, Lemij HG, et al. Baerveldt glaucoma implant in paediatric patients. Br J Ophthalmol. 2006;90:328–32.
17. Ishida K, Mandal AK, Netland PA. Glaucoma drainage implants in pediatric patients. Ophthalmol Clin North Am. 2005;18:431–42.
18. Beck AD, Freedman S, Kammer J, et al. Aqueous shunt devices compared with trabeculectomy with Mitomycin-C for children in the first two years of life. Am J Ophthalmol. 2003;136:994–1000.

19. Autrata R, Rehurek J. Long-term results of transscleral cyclophotocoagulation in refractory pediatric glaucoma patients. Ophthalmologica. 2003;217: 393–400.
20. Bock CJ, Freedman SF, Buckley EG, et al. Transscleral diode laser cyclophotocoagulation for refractory pediatric glaucomas. J Pediatr Ophthalmol Strabismus. 1997;34:235–9.
21. Kirwan JF, Shah P, Khaw PT. Diode laser cyclophotocoagulation: role in the management of refractory pediatric glaucomas. Ophthalmology. 2002;109:316–23.
22. Plager DA, Neely DE. Intermediate-term results of endoscopic diode laser cyclophotocoagulation for pediatric glaucoma. J AAPOS. 1999;3:131–7.
23. Gunja N, Varshney K. Brainstem anaesthesia after retrobulbar block: a rare cause of coma presenting to the emergency department. Emerg Med Australas. 2006;18:83–5.
24. Tatum PL, Defalque RJ. Subarachnoid injection during retrobulbar block: a case report. AANA J. 1994;62:49–52.
25. Moorthy SS, Zaffer R, Rodriguez S, et al. Apnea and seizures following retrobulbar local anesthetic injection. J Clin Anesth. 2003;15:267–70.
26. Nicoll JM, Acharya PA, Ahlen K, et al. Central nervous system complications after 6000 retrobulbar blocks. Anesth Analg. 1987;66:1298–302.
27. Edge KR, Nicoll JM. Retrobulbar hemorrhage after 12,500 retrobulbar blocks. Anesth Analg. 1993;76:1019–22.
28. Hamilton RC. Retrobulbar hemorrhage after retrobulbar blocks. Anesth Analg. 1994;78:608.
29. Noecker RJ, Kelly T, Patterson E, et al. Diode laser contact transscleral cyclophotocoagulation: getting the most from the G-probe. Ophthalmic Surg Lasers Imaging. 2004;35:124–30.
30. Carrillo MM, Trope GE, Chipman ML, et al. Repeated use of transscleral cyclophotocoagulation laser G-probes. J Glaucoma. 2004;13:51–4.
31. Tham CC, Lai JS, Fung PC, et al. Physical effects of reuse and repeated ethylene oxide sterilization on transscleral cyclophotocoagulation laser G-probes. J Glaucoma. 2002;11:21–5.
32. Nasisse MP, McGahan MC, Shields MB, et al. Inflammatory effects of continuous-wave neodymium: yttrium aluminum garnet laser cyclophotocoagulation. Invest Ophthalmol Vis Sci. 1992;33:2216–23.
33. Schuman J, Bellows A, Shingleton B, et al. Contact transscleral Nd:YAG laser cyclophotocoagulation. Midterm results. Ophthalmology. 1992;99:1089–94.
34. Dickens C, Nguyen N, Mora J, et al. Long-term results of noncontact transscleral neodymium: YAG cyclophotocoagulation. Ophthalmology. 1995;102: 1777–81.
35. Shields M, Shields S. Noncontact transscleral Nd:YAG cyclophotocoagulation: a long-term follow-up of 500 patients. Trans Am Ophthalmol Soc. 1994;92:271–83.
36. Wright M, Grajewski A, Feuer W. Nd:YAG cyclophotocoagulation: outcome of treatment for uncontrolled glaucoma. Ophthalmic Surg. 1991;22:279–83.
37. Hampton C, Shields M, Miller K, et al. Evaluation of a protocol for transscleral neodymium: YAG cyclophotocoagulation in one hundred patients. Ophthalmology. 1990;97:910–7.
38. Trope G, Ma S. Mid-term effects of neodymium: YAG transscleral cyclocoagulation in glaucoma. Ophthalmology. 1990;97:73–5.
39. Schlote T, Grüb M, Kynigopoulos M. Long-term results after transscleral diode laser cyclophotocoagulation in refractory posttraumatic glaucoma and glaucoma in aphakia. Graefes Arch Clin Exp Ophthalmol. 2007;246:405–10.
40. Puska PM, Tarkkanen AH. Transscleral red laser cyclophotocoagulation for the treatment of therapy-resistant inflammatory glaucoma. Eur J Ophthalmol. 2007;17:550–6.
41. Goldenberg-Cohen N, Bahar I, Ostashinski M, et al. Cyclocryotherapy versus transscleral diode laser cyclophotocoagulation for uncontrolled intraocular pressure. Ophthalmic Surg Lasers Imaging. 2005;36:272–9.
42. Ocakoglu O, Arslan OS, Kayiran A. Diode laser transscleral cyclophotocoagulation for the treatment of refractory glaucoma after penetrating keratoplasty. Curr Eye Res. 2005;30:569–74.
43. Lin P, Wollstein G, Glavas IP, et al. Contact transscleral neodymium: yttrium-aluminum-garnet laser cyclophotocoagulation: long-term outcome. Ophthalmology. 2004;111:2137–43.
44. Maus M, Katz LJ. Choroidal detachment, flat anterior chamber, and hypotony as complications of neodymium: YAG laser cyclophotocoagulation. Ophthalmology. 1990;97:69–72.
45. Kosoko O, Gaasterland D, Pollack I, et al. Long-term outcome of initial ciliary ablation with contact diode laser transscleral cyclophotocoagulation for severe glaucoma. The Diode Laser Ciliary Ablation Study Group. Ophthalmology. 1996;103:1294–302.
46. Lam S, Tessler H, Lam B, et al. High incidence of sympathetic ophthalmia after contact and noncontact neodymium: YAG cyclotherapy. Ophthalmology. 1992;99:1818–22.
47. Bechrakis N, Muller-Stolzenburg N, Helbig H, et al. Sympathetic ophthalmia following laser cyclocoagulation. Arch Ophthalmol. 1994;112:80–4.
48. Edward D, Brown S, Higginbotham E, et al. Sympathetic ophthalmia following neodymium: YAG cyclotherapy. Ophthalmic Surg. 1989;20:544–6.
49. Pastor S, Iwach A, Nozik R, et al. Presumed sympathetic ophthalmia following Nd:YAG transscleral cyclophotocoagulation. J Glaucoma. 1993;2:30–1.
50. Brancato R, Carassa R, Bettin P, et al. Contact transscleral cyclophotocoagulation with diode laser in refractory glaucoma. Eur J Ophthalmol. 1995;5: 32–9.

Procedural Treatments: Trabeculectomy

35

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Core Messages

- Limbus-based and fornix-based approaches to trabeculectomy have different advantages.
- Antimetabolite use is routine with trabeculectomy, although there are exceptions where its use can be withheld.
- Simple modifications to technique can minimize severe antimetabolite-related complications such as hypotony and cystic blebs and maximize clinical outcomes.

35.1 Which Is Better, a Limbus-Based Trabeculectomy or a Fornix-Based Trabeculectomy?

Important factors to consider in approaching trabeculectomy surgery include ease of surgical technique, risk of complication, and ultimate control of intraocular pressure (IOP). In trabeculectomy, the initial conjunctival incision can be created either at the limbus or in the fornix. This results in two different surgical approaches:

(a) A limbal-based conjunctival flap (LBCF)—incision in the fornix with the base at the limbus and
(b) A fornix-based conjunctival flap (FBCF)—incision is at the limbus with the base in the fornix. Cairns introduced the LBCF in his original description of trabeculectomy [1]. The FBCF was suggested later by Luntz in 1980 [2]. Luntz's aim was to have a surgical approach that offered better visualization of the scleral flap during construction, and he felt that the FBCF resulted in more posteriorly located blebs. Bleb characteristics that are considered desirable include a low, diffuse profile, flow that is directed posteriorly over a large surface area, and some vascularity, so that the bleb does not break down easily.

Both the LBCF and FBCF techniques have been adopted the world over, and each approach

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appears to have distinct advantages and drawbacks. A comparison by Shuster et al. demonstrated similar surgical success between limbus-based and fornix-based approaches, although early postoperative wound leaks were found more frequently with the fornix-based incisions. Despite this finding, they felt that the use of a fornix-based approach was advantageous, particularly for glaucomas typically associated with poor surgical success [3]. Bleb morphology between the two techniques was studied by Agbeja and Dutton [4], who identified that blebs in the FBCF group were more diffuse and demonstrated no higher frequency of wound leaks. A comparison of the two techniques by Grehn et al. [5] reported no difference in terms of IOP control, bleb morphology, visual field changes, and visual acuity. Another study suggested better IOP control with LBCF, but the study suffered from possible sample bias [6].

The introduction of routine antimetabolite use with trabeculectomies, especially mitomycin-C (MMC), generated concern regarding the tendency for postoperative wound leaks using FBCF. Henderson et al. [7] reported significantly more leaks (both spontaneous and provoked) with fornix-based incisions than with limbal-based incisions (65 % vs. 24 %), but they pointed out that the final outcome of the trabeculectomy was not adversely affected by these leaks. Another study compared the outcomes of trabeculectomy augmented with MMC using limbal- and fornix-based incisions and found no difference in IOP control, rate of aqueous leakage, or the need for intervention and glaucoma medications [8].

A very thin, cystic bleb is undesirable, as it is more prone to late leaks and blebitis. Our clinical observations suggest that there are two factors that lead to these undesirable blebs: anterior aqueous drainage and a ring of scar tissue that has been named the "ring of steel." LBCFs whose incisions are located more anteriorly are more likely to result in a cystic bleb, in part due to scar formation around the posterior incision site contributing to a "ring of steel." The "ring of steel" can be minimized by treating a larger scleral surface area with MMC, which is technically easier to do with a limbus-based conjunctival flap. Postoperative bleb morphology was studied by our group in young patients undergoing trabeculectomy with a high dose of MMC. A significantly higher number of cystic blebs was found in the limbus-based group (90 %) compared to the fornix-based group (29 %). There was also a remarkable difference in bleb-related complications between groups including late leakage, blebitis, and endophthalmitis—20 % for limbus-based blebs and 0.5 % for fornix-based blebs [9]. The advantages and disadvantages of both FBCF and LBCF are summarized in Table 35.1.

Table 35.1 Advantages and disadvantages of fornix-based and limbal-based conjunctival flaps

	Fornix-based conjunctival flap	Limbal-based conjunctival flap
Technical difficulty	Easier and faster surgical time	More difficult and longer surgical time
	Easily performed without assistant	Surgical assistant more important
Exposure of operative field	Good exposure allows good visualization of sclerostomy and easier placement of "releasable" sutures	Exposure more difficult to obtain with less visualization of sclerostomy. Reflected conjunctiva may make releasable suture placement difficult
Area to be dissected	Smaller	Larger
Antifibrotic application	Need great care on insertion, may need more sponges	Easier antifibrotic sponge application
Reoperation	Easier	More difficult due to posterior scarring
Bleb morphology	More diffuse in shape and drain more posteriorly	May get cystic blebs and "ring of steel" with drainage limited to anterior area
Conjunctival wound leakage	May have higher incidence of early leaks but published results are variable. Almost eliminated with corneal conjunctival or limbal frill closure technique	May have less early wound leaks

Summary for the Clinician

- There are many advantages to FBCFs, including an easier surgical exposure without a surgical assistant, more diffuse blebs that drain posteriorly because they are not limited by scar tissue in the fornix (the "ring of steel"), and easier reoperation.
- Advantages of limbus-based conjunctival flaps are that there may be fewer early wound leaks and antifibrotic application can be easier.

35.2 Should Antimetabolites Be Used in All Cases of Trabeculectomy?

In trabeculectomy, the main factor that determines long-term success is modulation of tissue healing. A fine balance between excessive flow and scarring is essential for optimal IOP results. This process of tissue repair can be modulated by various agents, as illustrated in Table 35.2. Today, two antimetabolite agents, mitomycin-C (MMC) and 5-fluorouracil (5-FU), are used regularly during surgery because they have been shown to significantly improve the success rate of trabeculectomy [10]. Several large randomized trials in the UK, Africa, and Singapore have shown that intraoperative use of 5-FU for 5 min on a sponge is safe to use in lower risk patients having first time surgery. 5-FU increases the success rate of trabeculectomies without any statistically significant increase in complications. Most surgeons favor MMC over 5-FU, as MMC is more likely to achieve target IOP long term, with a similar short-term safety profile as compared to 5-FU [11]. However, studies have shown that antimetabolite use may be associated in the long term with a higher rate of bleb leaks (both early and late), infections, hypotony, hypotony-related complications, and scleral melts.

Although in most cases use of an antimetabolite is recommended, there are exceptions to this rule. In patients with very thin conjunctiva or sclera or in high mopes, the use of antimetabolites may be relatively contraindicated.

Table 35.2 Intraoperative antiscarring agents applied directly to the bleb site

	5-FU	β-Radiation	MMC
	25 or 50 mg/mL	1000 cGy	0.2–0.5 mg/mL
Delivery	2–5 min	20 s to 3 min depending on output rate	1–5 min
Primary effect	Growth arrest	Growth arrest	Cell death
Control over area treated	Moderate	Precise	Moderate

Summary for the Clinician

- Tissue healing may be modulated with antimetabolites to improve outcomes of trabeculectomy.
- Antimetabolites are in common use for almost all trabeculectomies.
- The complications associated with antimetabolite use can be minimized by the use of safer surgical techniques, e.g., Moorfields Safer surgery system.

35.3 Do You Adjust Antimetabolite Usage and Dose Based on Patient Age or Race?

The choice of antifibrotic agent and treatment duration should be tailored according to patient risk factors, which are shown in Table 35.3. To some extent, dosage and duration also depend on the surgeon's experience with their own patient population. Elderly patients appear to have thinner tissues with a lower capability for vigorous healing. On the other hand, young patients, and especially children, are at higher risk for robust scarring due to very active ocular tissue healing.

Therefore, the use of antiscarring agent should be titrated depending on a patient's age.

Ethnic variations also affect the failure rate. Patients of African-Caribbean origin are prone to aggressive scarring and may require higher doses of antimetabolites (MMC up to 0.5 mg/mL). Similarly, in patients originating from the Indian subcontinent a higher rate of failure due to scarring is observed. Hispanic, Japanese, and Chinese populations have a risk of failure that is intermediate between the higher risk Afro-Caribbean population and lower risk White Caucasian population.

In addition to intrinsic patient characteristics of age and ethnicity, postoperative failure may be affected by presence of preexisting scar and activated tissue, such as from prior incisional surgery. This should also be taken into account when estimating dosage needed. Conjunctival inflammation also promotes scarring; thus, modifiable risk factors such as reaction to eye drops and blepharitis should be addressed preoperatively,

We use intraoperative MMC 0.2 mg/mL for lower risk patients and MMC 0.5 mg/mL for high-risk patients, all applied for 3 min. We do not vary the time of exposure, as previous pharmacokinetic studies we performed suggested that uptake was exponential until about 3 min, after which it plateaued rapidly (Fig. 35.1). Small changes in exposure time during the exponential phase would be very likely to result in large variations in the dose delivered [12].

Table 35.3 Age and ethnicity as risk factors for failure due to scarring after trabeculectomy

Patient	Risk 1–3+
Elderly adult	(+)
Young adult	+ (+)
Children	+ +
Children (presentation at birth)	+ + +(+)
Afro–Caribbean origin	+ +
May vary according to geographic area, e.g., West vs. East Africans	+ ++ (+)
Indian subcontinent origin	+
Hispanic origin	+
Japanese origin	+
Asian/Chinese origin	(+)

( ) = Some controversy in the literature

Summary for the Clinician

- Pharmacokinetic data has shown that uptake of antimetabolite is exponential until approximately 3 min, suggesting that the concentration rather than the duration of contact should be varied.
- Higher risk categories for bleb failure include darker skin, younger age, previous conjunctival surgery, and inflamed eyes.
- In high-risk patients, the dose of antimetabolite can be higher, while in lower risk patients a lower dose can be used.

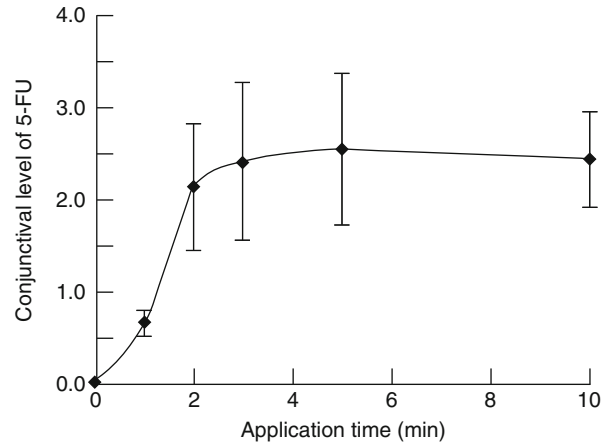

Fig. 35.1 Graph showing plateau of tissue antimetabolite uptake after 3 min. Up to 2 min, there is exponential uptake during which small variations in timing can result in marked variations in uptake (From [12])

35.4 What Different Techniques Can I Utilize to Apply Mitomycin-C?

MMC is now widely used in trabeculectomy. Different application techniques have been described, with variable results and complications. It is very important for every surgeon to familiarize himself/herself with one particular technique and to build up experience with it, in order to increase efficacy and minimize complications. MMC is an extremely potent antimetabolite that should be treated with caution and respect, as it can irreversibly damage the sclera and the cornea, even in small doses [13].

If applying mitomycin-C via a pledget, in both limbus- and FBCFs, meticulous dissection with Westcott scissors is required, to create a pocket into the supra-scleral/sub-Tenon's plane measuring approximately $10^{-15} \times 10^{-15}$ mm. This will produce a large area for antifibrotic treatment, allowing uninterrupted posterior flow. Further dissection of Tenon's capsule and exposure of bare sclera can be achieved with the use of a Tooke's knife (Altomed, Ltd, Boldon, UK) (see Fig. 35.2).

Many surgeons apply MMC underneath the conjunctiva alone before scleral flap construction. At Moorfields, MMC is usually delivered underneath both the conjunctiva and scleral flaps, as we find that this results in significantly lower IOP with no increase in complications in our patient population [14]. There was an initial concern regarding possible intraocular drug entry with sub-scleral flap treatment; however, pharmacokinetic and clinical data now suggest that sub-scleral application can be done safely [14]. To minimize the risk of intraocular penetration, it is preferable to apply antifibrotics after constructing the scleral flap but before entry into the anterior chamber. If the scleral integrity has been breached or there is any sign of aqueous leak from an early anterior chamber entry, the use of antifibrotics should be withheld to prevent antimetabolites from entering the anterior chamber.

The conjunctiva can be held back with special conjunctival clamps (e.g., Duckworth-and-Kent. com T clamp No 2–686), so that the edges are not directly exposed to MMC, which might cause subsequent leakage from the limbus in a fornix-based flap (Fig. 35.3).

We prefer to deliver MMC into the sub-Tenon's pocket with medical-grade polyvinyl alcohol (PVA) sponges (Merocel, Medtronics, Inc., Minneapolis, MN), sold as LASIK corneal shields, rather than with methylcellulose sponges because PVA sponges maintain their integrity and do not fragment, thereby reducing the chance of leaving residual microdebris, which can cause foreign-body granulomas [15]. The PVA sponges can be cut in half (Fig. 35.4) to approximately 5×3 mm before inserting into the pocket (up to six pieces). Alternatively, a series of smaller sponges cut to various dimensions, a single large sponge (for example, 8×10 mm) on a stick or free, or filter paper strips soaked in MMC can be inserted, if appropriate. A commercially licensed version of MMC 0.2 mg/mL is now available where the MMC is reconstituted in a sealed chamber with precut sponges before application. There are many variations of MMC application via pledget.

A key concept for safer MMC application is to maximize the area of antiscarring effect between the conjunctival and scleral plane, while minimizing contact with structures that may be damaged, such as the cornea or the free conjunctival edge. To achieve this end, two methods are commonly used with success: pre-soak sponges in MMC, squeeze excess off the sponges, and place the sponges in the desired space while taking care to avoid contact with free conjunctival edges and cornea; alternatively, one can place dry sponges in the subconjunctival/sub-Tenon space and inject MMC onto the sponges, taking care not to inject excess which can spill onto delicate

Fig. 35.2 Tookes knife by Altomed Ltd, Boldon Business, England

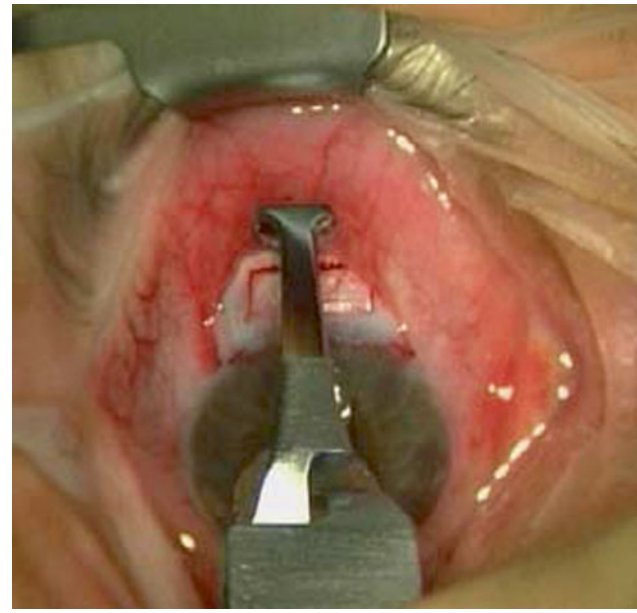

Fig. 35.3 Khaw conjunctival T clamp for holding tissue away from antimetabolite

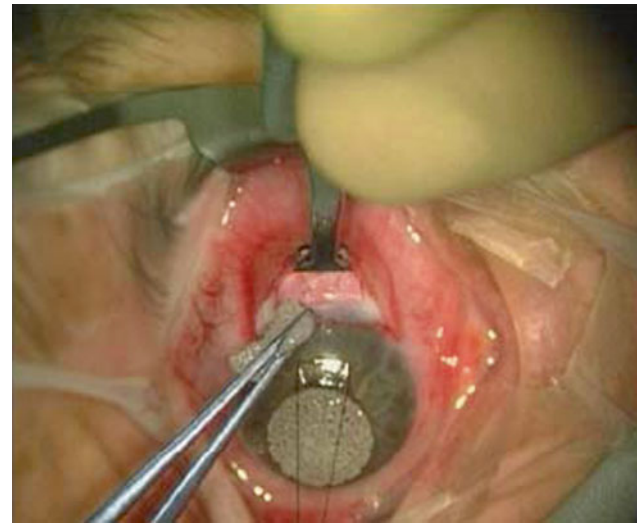

Fig. 35.4 Polyvinyl alcohol sponges being folded in order to avoid contact with the cut edge of conjunctiva

surrounding structures. Typically, 0.2 mL of 0.2–0.5 mg/mL MMC for 3 min is necessary, although the volume may vary and should be judged intraoperatively. Table 35.3 summarizes the risks to consider when determining the strength of dose needed. We do not advocate mixing lidocaine with mitomycin, as the anesthetic used for surgical procedure should be sufficient. If analgesia is a concern, additional sub-Tenon or subconjunctival block with marcaine can be administered at the end of the surgery.

It is imperative that the treatment area is as large as possible in order to create a diffuse, noncystic bleb and to prevent the development of a posterior limiting scar ("ring of steel"). Immediately following sponge removal (count sponges as they go in and come out), the treated area, along with the conjunctiva and the cornea,

is copiously irrigated with 20 mL of BSS (balanced salt solution).

MMC is also being delivered as a preoperative subconjunctival injection immediately before trabeculectomy. If this is done, great care has to be exercised as one drop of MMC in the anterior chamber causes irreversible endothelial failure and corneal opacification. To minimize the risk of this occurring the injection should be given as far posteriorly into the fornix and as superficially as possible (needle bevel visible at all times) and then the fluid swept forward gently to the desired area. More than one injection of MMC leads to avascular changes in the conjunctiva. If possible, avoid injecting MMC directly into an incision area.

Summary for the Clinician

- Antimetabolites can be applied with various surgical sponges or filter paper strips, or it may be injected into the subconjunctival space.
- Different pledget materials used to apply antimetabolites may release different amounts of antimetabolite—a surgeon should develop experience and expertise with one technique.
- A large area of conjunctiva should be exposed to treatment with antimetabolite to achieve a diffuse noncystic bleb.
- Care has to be taken to avoid treating the conjunctival wound edge to the antimetabolite.

35.5 Intraoperatively, What Can I Do Technically to Ensure the Best Surgical Outcome?

Trabeculectomy technique has evolved over the last decade. It is now feasible to create an efficient and safe filtration system, following certain principles at each step of the procedure:

- *Position of filtration area*. Preoperatively, the lid position should be noted in relation to the superior limbus, to ensure that the bleb is covered under the upper lid. It may be useful to mark the lid position on the limbus at the time of surgery. An interpalpebral bleb considerably increases the incidence of discomfort and bleb-related complications, such as leak and infection.
- *Traction suture*. A corneal traction suture (7–0 black silk or nylon suture are commonly used) exerts more traction than a superior rectus bridle suture and avoids the possible formation of a superior rectus hematoma. The CAT152 clinical trial showed that using a bridle suture around the rectus muscle was a risk factor for trabeculectomy failure [16].
- *Conjunctival incision*. Fornix-based flaps provide better exposure of the sclera and decrease the chances of a posterior scar developing that will restrict aqueous flow. Relaxing incisions at the ends of the limbal wound in FBCFs are not necessary, but can sometimes be helpful to increase exposure.
- *Scleral flap*. The scleral flap must be sufficiently large and of substantial thickness to provide resistance to aqueous outflow, especially if antimetabolites are used. This is also extremely important in eyes with thin, less rigid sclera as seen in buphthalmos and high myopia. Thin flaps lead to a high-risk of excessive aqueous filtration and hypotony. On the flap, the side incisions (parallel if flap is a square or slanted if flap is a triangle) that come from the limbus are not cut right up to the limbus, but are left incomplete (1–2 mm from limbus). This encourages posterior flow and forces the aqueous posteriorly over a wider area to help achieve a diffuse bleb. Scleral flap sutures can be pre-placed while the eye is still firm, because at times it is much more difficult to place them once the eye becomes hypotonous after anterior chamber entry.
- *Area of antimetabolite treatment*. The largest possible area should be treated in order to prevent the formation of a posterior limiting scar ("ring of steel").
- *Scleral sutures*. Adjustable or releasable sutures allow postoperative adjustment of the IOP. The initial postoperative IOP target should be slightly higher than what is actually

desired to enable manipulation of the filtration system and avoid the dreadful postoperative complication of hypotony due to hyperfiltration. The ideal tension of the scleral sutures is one that allows slow egress of aqueous fluid at the edges of the scleral flap while maintaining a deep anterior chamber intraoperatively.

- *Infusion*. An anterior segment infusion system (Lewicky, BD Visitec, Franklin Lakes, NJ) through the paracentesis with a three-way tap can stabilize the IOP during surgery and decrease the risk of serious complications such as intraoperative choroidal effusions. With this system, the aqueous flow can be titrated by increasing or decreasing the bottle height, enabling more accurate suturing of the scleral flap.
- *Conjunctival closure*. The conjunctiva should be sutured meticulously, to ensure that it remains watertight, especially if antimetabolites have been used. There are many variations of conjunctival closure. Some work better for individual surgeons than others. For a fornix-based flap, we place lateral purse string sutures at either end of the limbus or relaxing incisions (if present), along with interrupted mattress sutures between the conjunctiva and the cornea. Several corneal grooves are made to bury the mattress suture knots into the cornea to avoid discomfort from the nylon sutures. Alternatively, a frill of conjunctiva can be left at the limbus to help create a watertight closure.

The above technique, with special attention to surface area of MMC treatment, conjunctival and scleral flap construction, and adjustable sutures, has resulted in a dramatic reduction of complications, such as hypotony, cystic blebs, blebitis, and endophthalmitis, for our group. Each surgeon should adopt techniques that work well in his/her hands and then perfect that technique to ensure the most reliable, repeatable outcomes possible.

Summary for the Clinician

- Traction sutures are associated with better outcomes than superior rectus bridle sutures.
- The scleral flap must be of sufficient thickness and size to provide resistance to aqueous flow.
- The area of antimetabolite treatment should be large.
- Scleral sutures can be placed so as to be permanent with the option of laser suture lysis postoperatively, or they can be tied as releasable or adjustable sutures.
- An anterior segment infusion system can be helpful in preventing anterior chamber collapse and titrating the tension on scleral flap sutures.
- Conjunctival closure has many variations but should be meticulous in all cases.

35.6 When Should I Use Adjustable Sutures? When Should I Use Laser Suture Lysis?

The scleral flap can be sutured either with (a) fixed interrupted sutures that can be lasered later, (b) releasable sutures, which can be pulled out postoperatively, or (c) adjustable sutures that can be loosened transconjunctivally. Our preferred technique is a combination of all suture types, thus taking advantage of the benefits and ameliorating the shortcomings of each. We advocate the initial placement of a fixed suture (10–0 nylon) at the temporal posterior corner of the scleral flap, one releasable at the nasal posterior corner, and one adjustable at the posterior edge (Fig 35.5). Controlling the infusion through the paracentesis while observing the amount of aqueous flow through the flap aids in the assessment for further sutures.

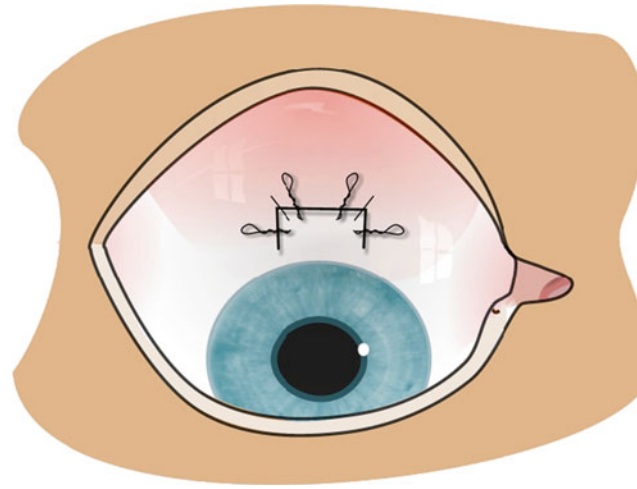

Fig. 35.5 Diagram showing fixed (*left*), adjustable (*middle*), and releasable sutures

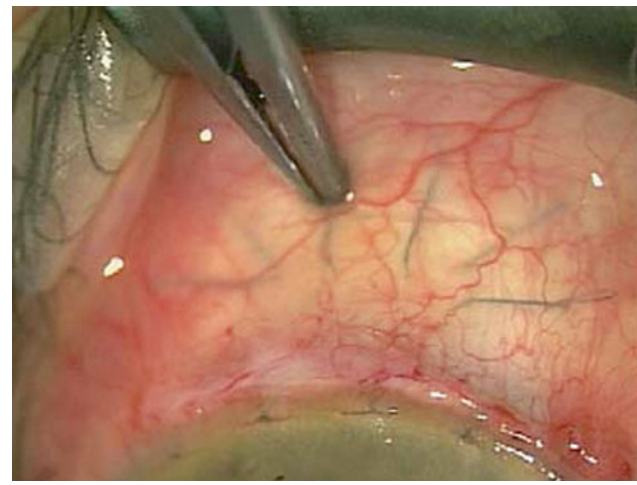

Fig. 35.6 10–0 Nylon fixed sutures at each posterior corner of the scleral flap. Four adjustable sutures are seen through the conjunctiva. In this postoperative photograph, the adjustable sutures are being manipulated transconjunctivally, thereby loosening the sutures and increasing flow through the scleral flap

The fixed suture is beneficial for its ease of placement intraoperatively, and its security in patients who are prone to eye rubbing, such as children; however, they require laser suture lysis which can be difficult for those unable to sit still at the slit lamp. In contrast, the releasable suture can be removed with relative ease, but requires more time intraoperatively. The adjustable suture combines ease of intraoperative placement with the added benefit of a finer degree of adjustment of postoperative IOP than complete lysis or suture removal. Adjustable sutures allow postoperative manipulation of the bleb by transconjunctival loosening (Fig. 35.6) with a special forceps (it is not lasered or pulled out). The adjustable suture is created by making four throws on a loop (Fig. 35.7). The forceps used for postoperative adjustment is the Khaw transconjunctival adjustable suture forceps (2–502 Duckworth and Kent, Baldock, England). Releasable sutures require a corneal loop, which can be accessed later for removal, followed by four throws on a loop (Fig 35.8).

Laser suture lysis of fixed sutures using a compression contact lens (e.g., Hoskins, Ritch, or Blumenthal lens) is another method of suture

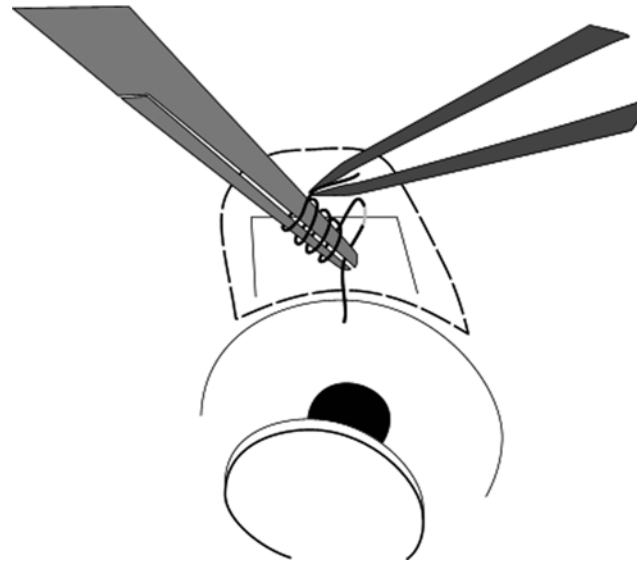

Fig. 35.7 Diagram showing the four throws of the adjustable suture. The loop is pulled through and tightened as required and that completes the suture. This suture is tied using standard forceps. The suture is adjusted using a Khaw adjustable forceps

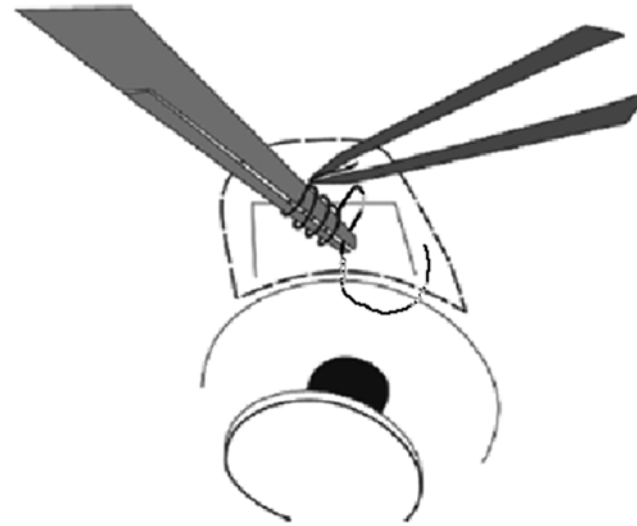

Fig. 35.8 Diagram showing the releasable suture with corneal segment that can be grasped later during suture removal. Suture can be tied by pulling loop through four throws and tightening

manipulation for inadequate aqueous flow in the early postoperative period. One risk of suture lysis is the formation of a buttonhole in the conjunctiva if the laser power used is very high. Buttonholes rarely occur with green argon laser settings of 50 mm spot size, 0.1 s duration, and 200–400 mW.

Whichever technique is used to facilitate increased aqueous outflow postoperatively, it is imperative to be aware that hypotony can result from suture manipulation even several months after surgery (although the greatest risk for this is in the first few postoperative weeks) because of the prolonged inhibition of subconjunctival scarring with antimetabolite therapy, especially with MMC. During the first few weeks after surgery when lysing or releasing a suture poses the highest risk of hypotony, adjustable sutures are particularly advantageous for fine control of IOP. For this reason, we use adjustable sutures in all cases and find that a small amount of xylocaine and adrenaline subconjunctivally is occasionally required for the adjustment of sutures in particularly sensitive patients.

Summary for the Clinician

- The choice of scleral flap suture technique is up to the individual surgeon, the availability of the necessary equipment to lyse, pull, or adjust sutures, and the desired degree of flow adjustment of the trabeculectomy.

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References

1. Cairns JE. Trabeculectomy. Preliminary report of a new method. Am J Ophthalmol. 1968;66:673–9.
2. Luntz MH. Trabeculectomy using a fornix-based conjunctival flap and tightly sutured scleral flap. Ophthalmology. 1980;87:985–9.
3. Shuster JN, Krupin T, Kolker AE, Becker B. Limbus- vs. fornix-based conjunctival flap in trabeculectomy. A long-term randomized study. Arch Ophthalmol. 1984;102:361–2.
4. Agbeja AM, Dutton GN. Conjunctival incisions for trabeculectomy and their relationship to the type of bleb formation—a preliminary study. Eye (Lond). 1987;1(Pt 6):738–43.
5. Grehn F, Mauthe S, Pfeiffer N. Limbus-based versus fornix-based conjunctival flap in filtering surgery. A randomized prospective study. Int Ophthalmol. 1989;13:139–43.
6. Reichert R, Stewart W, Shields MB. Limbus-based versus fornix-based conjunctival flaps in trabeculectomy. Ophthalmic Surg. 1987;18:672–6.
7. Henderson HW, Ezra E, Murdoch IE. Early postoperative trabeculectomy leakage: incidence, time course, severity, and impact on surgical outcome. Br J Ophthalmol. 2004;88:626–9.
8. Alwitry A, Patel V, King AW. Fornix vs. limbal-based trabeculectomy with mitomycin C. Eye (Lond). 2005;19:631–6.
9. Wells AP, Cordeiro MF, Bunce C, Khaw PT. Cystic bleb formation and related complications in limbus- versus fornix-based conjunctival flaps in pediatric and young adult trabeculectomy with mitomycin C. Ophthalmology. 2003;110:2192–7.
10. Palanca-Capistrano AM, Hall J, Cantor LB, Morgan L, et al. Long-term outcomes of intraoperative 5-fluorouracil versus intraoperative mitomycin C in primary trabeculectomy surgery. Ophthalmology. 2009;116:185–90.
11. Singh K, Egbert PR, Byrd S, et al. Trabeculectomy with intraoperative 5-fluorouracil vs. mitomycin C. Am J Ophthalmol. 1997;123:48–53.
12. Wilkins M, Occlusion N, Waters L, Kotecha A, Khaw PT. Effects of sponge type, size and application technique on tissue levels of 5-fluorouracil. Br J Ophthalmol. 2000;84:92–7.
13. Sauder G, Jonas JB. Limbal stem cell deficiency after subconjunctival mitomycin C injection for trabeculectomy. Am J Ophthalmol. 2006;141:1129–30.
14. You YA, Gu YS, Fang CT, Ma XQ. Long-term effects of simultaneous subconjunctival and subscleral mitomycin C application in repeat trabeculectomy. J Glaucoma. 2002;11:10–118.
15. Poole TR, Gillespie IH, Knee G, Whitworth J. Microscopic fragmentation of ophthalmic surgical sponge spears used for delivery of ant proliferative agents in glaucoma filtering surgery. Br J Ophthalmol. 2002;86:1448–9.
16. Edmunds B, Bunce CV, Thompson JR, et al. Factors associated with success in first-time trabeculectomy for patients at low risk of failure with chronic open-angle glaucoma. Ophthalmology. 2004;111:97–103.

Procedural Treatments: Perioperative Medication

36

Simon K. Law

Core Messages

- Topical glaucoma therapy is associated with inflammatory and atypical changes of the conjunctiva.
- Topical glaucoma therapy may contribute to the failure of trabeculectomy by inducing a conjunctival inflammatory response and reducing aqueous outflow.
- Steroids are a mainstay of postoperative care in glaucoma surgery.
- Topical antibiotics can be used perioperatively in glaucoma surgery; their chronic use does not prevent endophthalmitis or blebitis after trabeculectomy.
- Hemorrhagic complications following glaucoma surgery are associated with acute reduction in IOP and hypotony, as well as with oral anticoagulation therapy.

36.1 Should Topical Glaucoma Medication Be Discontinued Before Performing Trabeculectomy?

Inflammation plays a significant role in the success of glaucoma surgery. It has been shown that chronic use of topical glaucoma therapy is associated with inflammatory and atypical changes of the conjunctiva. In a study from 2008, conjunctival cells obtained from the ocular surface of patients receiving long-term glaucoma treatment demonstrated a significantly increased expression of inflammatory markers, suggesting that inflammatory mechanisms, both allergic and toxic, are at work on the ocular surface of these patients [1]. The response appears to be dose related. HLA-DR class II antigen, a hallmark of inflammation, was elevated significantly in patients receiving multiple therapies, whereas patients on monotherapies showed only slight and insignificant increases [1]. Indeed it is not uncommon for patients to be on 3–4 different topical medications for a long period of time before trabeculectomy is considered. In these patients, the third and fourth medications added may have minimal or no intraocular pressure (IOP) reduction effect, yet they may incrementally add to conjunctival inflammation (Fig. 36.1). Ideally, one would discontinue as many topical drops as possible prior to surgery to allow the ocular surface to return to a less inflamed state.

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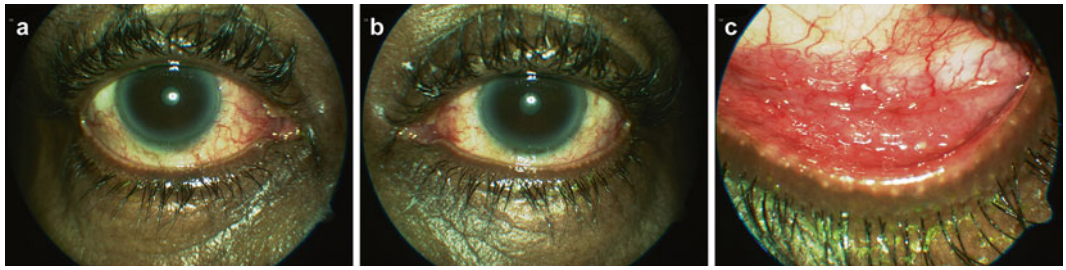

Fig. 36.1 Patient on three different topical medications for many years. (**a**) Right eye with hyperemia of the conjunctiva. (**b**) Left eye with hyperemia. (**c**) Follicular reaction of the palpebral lid indicates allergic inflammation. This inflammation can reduce the success of trabeculectomy if not first controlled by discontinuing the offending topical agent and starting preoperative steroids

If a drop is inducing an allergic reaction, the agent definitely should be discontinued prior to surgery. The effectiveness of a topical medication that is causing an allergic reaction is no longer reliable and the active inflammatory reaction is likely to adversely affect the outcome of the surgical procedure.

By minimizing the number of topical drops, one reduces the ocular surface's exposure to the toxicity of both active and inactive drop ingredients. In my practice I limit maximum medical therapy to 4–5 drops a day per eye. For patients requiring multiple medications to control IOP, I will typically use a prostaglandin analog once daily in addition to either fixed combination of timolol/dorzolamide and brimonidine twice daily, or fixed combination of timolol/brimonidine and dorzolamide twice daily, or fixed combination of dorzolamide/brimonidine twice daily and timolol daily. In countries where prostaglandin analog/beta-blocker combinations are available, the maximum number of daily drops may be adjusted accordingly. I seldom use miotics (except in aphakic/pseudophakic patients and in plateau iris syndrome) or oral carbonic anhydrase inhibitors, although they do have a role, for example, when topical therapy is not effective enough in reducing the IOP, as a last resort in patients who cannot tolerate topical therapy, or when surgical options need to be delayed or are contraindicated.

The success of trabeculectomy largely depends on the continuous flow of aqueous humor through the newly created surgical channel, which in turn depends on minimal adhesion and scarring of the scleral flap. The aqueous suppressing effect or uveoscleral outflow enhancing effect of topical or systemic medications may last for days to weeks after their discontinuation. These persistent effects may decrease aqueous flow through the newly created outflow channel. Despite this potentially detrimental effect to the outcome of trabeculectomy, often medications cannot be discontinued prior to surgery because of the high level of IOP in most of the glaucoma patients who require surgery. However, at the very least topical glaucoma therapy should be optimized by eliminating duplicate medications in the same class, medications with low effectiveness, or those inciting an allergic reaction. If the untreated IOP is not particularly high for the degree of optic nerve damage, for example in the low 20's, glaucoma medications may be held for a few days prior to surgery.

Summary for the Clinician

- Conjunctival inflammation may have detrimental effects on the success of trabeculectomy.
- Topical glaucoma medications induce inflammation of the ocular surface and this is probably a dose-related response.
- Clinicians should preserve the health of the ocular surface tissue by simplifying topical medical regimens, eliminating medications that are inducing allergic reactions, and replacing those that are ineffective.

36.2 What Preoperative and Postoperative Medications Are Needed for Trabeculectomy? How Long Should I Continue Topical Steroid and Antibiotics After Glaucoma Surgery?

Following trabeculectomy, topical steroid is a priority to control postoperative inflammation and to modulate the tissue healing process. Some surgeons ask patients to start topical steroids between 2 and 7 days before surgery in order to decrease any preexisting inflammation and to blunt the postoperative inflammatory response. Generally after a trabeculectomy, topical steroid (usually prednisolone acetate 1 %) is used at a frequency of one drop 4 times daily and tapered gradually over a period of 4–6 weeks, depending on the level of bleb hyperemia. However, topical steroid may need to be used or tapered over a longer time period in cases of combined cataract and glaucoma surgery or in an eye with a history of uveitis. The decision of how to taper is guided by the level of postoperative inflammation, as evidenced by conjunctival hyperemia and the anterior chamber cell. It is generally recognized by glaucoma specialists that chronic use of topical steroid may increase IOP in patients who are steroid responders, even in the presence of an apparently functioning conjunctival bleb.

Difluprednate 0.05 % ophthalmic emulsion is a potent topical corticosteroid that is indicated for the treatment of inflammation associated with ocular surgery. Its anti-inflammatory potency is close to 6 times that of prednisolone (or equivalent to dexamethasone). Therefore, the starting dose and tapering schedule of difluprednate are different from prednisolone and should be adjusted according to the level of postoperative inflammation. Since the potencies of different corticosteroids are compared by in vitro assay instead of in a model of ocular inflammation relevant to human disease, no conclusion can be made about the dissociation of anti-inflammatory and IOP-elevating effects. Although the rates of IOP elevation of difluprednate and prednisolone are similar in clinical trials on uveitis and postoperative inflammation, the IOP elevation associated with difluprednate 0.05 % can be more severe than with prednisolone acetate 1 %, especially in steroid responders in our experience [2].

An antibiotic drop is often used for 1 week postoperatively, but may be extended for a longer period of time if a wound leak is noted. Some surgeons do not use perioperative antibiotics for trabeculectomy. There is no data to support the use of perioperative antibiotics to prevent postoperative blebitis or endophthalmitis (which is rare immediately following trabeculectomy). There is also no data to support the chronic use of antibiotics in the prevention of late onset blebitis or endophthalmitis. In fact, chronic or intermittent use of topical antibiotics beyond the immediate postoperative period has been associated with an increased risk of bleb-related infections [3].

Summary for the Clinician

- Postoperative topical steroid is generally used for 4–6 weeks following trabeculectomy and may be started preoperatively to begin management of inflammation.
- A steroid response with increased IOP may occur even in the presence of a functional bleb.
- There is no data to support the chronic use of topical antibiotic in the prevention of endophthalmitis or blebitis after trabeculectomy.

36.3 Which Topical Steroid Should Be Used Perioperatively?

Among a number of topical steroid and antibiotic-steroid combination choices, prednisolone acetate 1 % is most commonly used in the management of inflammation following any intraocular procedures. There are many formulations of prednisolone acetate, both brand name and generic. Some generic formulations have been noted to suspend poorly in solution, cake, or precipitate and clog dropper tips [4]. When the

control of postoperative inflammation is a concern, I prefer my patient to use a brand name product such as Pred Forte 1 % (Allergan, Irvine, CA). I also instruct patients to shake the bottle before instillation. Another option is difluprednate 0.05 % ophthalmic emulsion, which does not require shaking the bottle before instillation. Its higher anti-inflammatory potency may allow a lower starting frequency or a quicker taper.

Summary for the Clinician

- Generic steroid drops may not be as effective in the control of postoperative inflammation.

36.4 If IOP Reduction Is Needed Following Glaucoma Surgery, What Topical Medication Is Most Effective in Lowering IOP and Safest for the Trabeculectomy? Are Prostaglandins Effective in IOP Reduction After Glaucoma Surgery?

The success of trabeculectomy to control IOP tends to decrease over time. When a scleral flap or bleb completely scars down and outflow ceases, the response of the eye to topical therapy may be similar to what it was prior to trabeculectomy. However, in the case of a semi-functional trabeculectomy where outflow is reduced, clinicians may observe a more variable response to topical therapy. Topical glaucoma therapy may not have the same effectiveness as in eyes without glaucoma surgery, and therefore therapy has to be individualized.

Summary for the Clinician

- The response to topical glaucoma therapy may be unpredictable in the presence of a semi-functional bleb.

36.5 How Should Anticoagulation and Antiplatelet Therapies Be Managed Perioperatively?

The typical patient presenting for glaucoma surgery is likely to be older and have comorbid conditions requiring chronic oral anticoagulation therapy or antiplatelet therapy. Chronic oral *anticoagulation therapy* with warfarin sodium is instituted for a variety of medical conditions including prosthetic heart valves, atrial fibrillation, ischemic heart disease, cerebrovascular disease, and venous thromboembolism [5]. Newly available oral anticoagulants (NOAs) that target key coagulation factors such as factors Xa or IIa (thrombin) include dabigatran, rivaroxaban, and apixaban are approved for similar indications and with similar anticoagulation effects and risks. *Antiplatelet therapy* with aspirin, clopidogrel, ticlopidine, or dipyridamole has established benefits in the secondary prevention of fatal and nonfatal coronary and cerebrovascular events [6, 7]. In my practice, 27 % of all patients who have undergone glaucoma surgery required anticoagulation or antiplatelet therapy. The three most common medical indications for anticoagulation therapy in my patient population are arrhythmia, status post cardiac valve replacement, and history of cerebral vascular accident.

The preoperative use of anticoagulation therapy or antiplatelet therapy in ophthalmic surgery is a risk factor for hemorrhagic complications associated with local anesthetic injections, intraoperative hemorrhage, or delayed postoperative hemorrhage. However, discontinuation of these therapies may predispose patients to a transient yet dangerous hypercoagulable state [8].

Despite the common use of these agents by patients who require ophthalmic surgery, there are no clear guidelines for their perioperative management. At the Jules Stein Eye Institute, we performed a comprehensive retrospective review of patients on chronic anticoagulation (warfarin) or antiplatelet therapy undergoing glaucoma surgery. Patients taking either therapy were matched case-by-case to patients who were not on such therapies to determine the incidence of and risk factors for hemorrhagic complications and the

rate of systemic complications, such as thromboembolic events. Patients on chronic anticoagulation therapy had a statistically significantly higher rate of hemorrhagic complications than patients on chronic antiplatelet therapy, and patients who continued anticoagulation therapy during glaucoma surgery had the highest rate of hemorrhagic complications. We were unable to determine if discontinuing these therapies prior to glaucoma surgery reduces the rate of hemorrhagic complications. An additional risk factor for hemorrhagic complications in patients on anticoagulation or antiplatelet aggregation therapy is a high preoperative IOP [9]. As shown in the Fluorouracil Filtering Surgery Study, acute reduction of a relatively high IOP during surgery or postoperative suture lysis has been shown to be associated with hemorrhagic complications [10].

In patients receiving chronic anticoagulation or antiplatelet therapy, those who experienced hemorrhagic complications during or after glaucoma surgery had a significantly higher rate of severe loss of vision. Therefore we believe that every effort should be made to minimize the risks of untoward bleeding in patients who are on anticoagulation or antiplatelet therapy, weighing the risk of systemic effects that also need to be kept to a minimum. If a patient is on chronic antiplatelet therapy alone (aspirin, clopidogrel, ticlopidine, or dipyridamole), we generally do not discontinue the therapy prior to the glaucoma surgery. In patients who are on chronic oral anticoagulation therapy, we collaborate closely with their primary care providers. In order to reduce the risk of bleeding complications, we prefer withholding warfarin at least 3 days prior to the glaucoma surgery if the risk of thromboembolic event is low. Since the half-life of NOAs is much shorter than warfarin's half-life, dabigatran, rivaroxaban, and apixaban may be withheld for just 1–2 days prior to surgery. However, in patients with poor renal function, NOAs may need to be stopped 3–4 days before surgery. Such a decision should always be communicated with and approved by the patient's internist or medical subspecialist. A preoperative coagulation profile including international normalized ratio (INR) should be checked the morning of surgery if the patient is taking warfarin. In healthy people, INR is usually 1.0. An INR less than 2.0 may not provide adequate protection from clotting, while an INR greater than 3.0 may create excessive risk of hemorrhagic complications. Dosing of NOAs generally does not require coagulation monitoring.

Following guidelines for general surgery, internists use the level of annual risk of thromboembolic stroke as a guidepost in making recommendations regarding anticoagulation/antiplatelet therapy changes. The guidelines are as follows: if the annual risk of thromboembolic stroke without anticoagulation is less than 4 %, such as in patients with atrial fibrillation without a history of thromboembolic stroke, withholding oral anticoagulation therapy prior to surgery is recommended. If the patient is at moderate risk (4–7 %) of thromboembolic stroke without anticoagulation, such as with a mechanical aortic valve, oral anticoagulation therapy may be withheld with optional administration of either intravenous treatment-dose heparin or subcutaneous low molecular weight heparin. If the annual risk is high (>7 %), such as with a mechanical mitral valve or atrial fibrillation with a history of thromboembolic stroke, withholding oral anticoagulation therapy and mandatory administration of either treatment-dose intravenous heparin or subcutaneous low molecular weight heparin is recommended [11]. Since the pharmacologic effect of heparin is shorter than that of warfarin, the coagulation status will at least be partially normalized during the surgery, minimizing hemorrhagic complications. The guidelines for perioperative management of antiplatelet therapy in general surgery are not as clear, but tend to follow a similar pattern as anticoagulation therapy.

We do not recommend following the anticoagulation/antiplatelet therapy guidelines for cataract surgery. Most patients can undergo cataract surgery without alteration of their regimen of anticoagulation therapy or antiplatelet therapy, since major bleeding while receiving therapeutic anticoagulation therapy is rare with cataract surgery [12]. However, cataract surgery may have a lower risk of hemorrhage by virtue of small clear corneal incision techniques and the use of topical

anesthesia when compared to glaucoma surgery. Patients undergoing glaucoma surgery often start with high IOP, experience a sudden drop in IOP or a period of hypotony, and may require an iridectomy; all of these factors pose an increased risk of intraoperative or delayed bleeding in the form of hyphema, vitreous or retinal hemorrhage, or choroidal hemorrhage [13–15].

If there are no hemorrhagic complications intraoperatively or postoperatively, oral anticoagulation therapy may be resumed the day following glaucoma surgery. However, if a major complication occurs, such as total hyphema or suprachoroidal hemorrhage, anticoagulation therapy may need to be withheld for a period of time while working closely with the patient's internist.

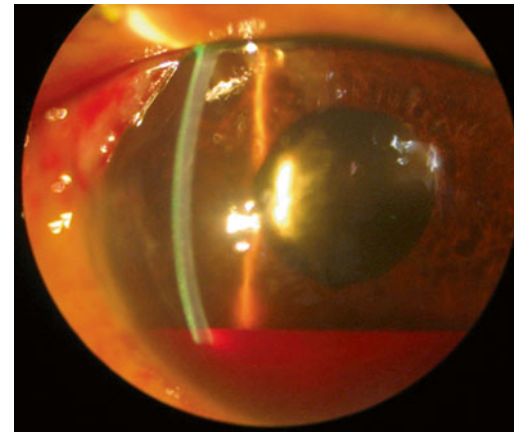

Fig. 36.2 Hyphema in the early postoperative period following a superotemporal fornix-based trabeculectomy with a diffuse bleb

Summary for the Clinician

- Glaucoma surgery carries a higher risk of hemorrhagic complications than cataract surgery and perioperative guidelines regarding antiplatelet and anticoagulation therapies should be followed.
- Antiplatelet therapy (aspirin, clopidogrel, ticlopidine, or dipyridamole) may be continued through glaucoma surgery.
- Oral anticoagulation therapy (warfarin, dabigatran, rivaroxaban, and apixaban) is associated with a higher rate of bleeding complications during and after glaucoma surgery than antiplatelet therapy.

36.6 Should Glaucoma Surgery Technique Be Modified to Reduce the Chances of Hemorrhagic Complications?

In the Fluorouracil Filtering Surgery Study, high preoperative IOP was identified as a statistically significant risk factor for delayed suprachoroidal hemorrhage [10]. In contrast, Tuli et al. found that postoperative hypotony was associated with a higher rate of delayed suprachoroidal hemorrhage [15]. One possible reason why high preoperative IOP and postoperative hypotony are both associated with delayed suprachoroidal hemorrhage after glaucoma surgery may be the radical reduction of IOP resulting from the operative procedure. Acute reduction of a relatively high IOP during surgery or postoperative suture lysis is known to be associated with hemorrhagic complications [10]. Lowering IOP gradually should be the goal. Lowering very high IOP in the preoperative holding area with systemic glaucoma therapy can be considered. A sudden IOP drop intraoperatively can be mitigated by using a small paracentesis, a tight scleral flap in trabeculectomy, a suture ligature or stent in a tube shunt procedure, or injection of viscoelastic material into the anterior chamber.

Bleeding from flap dissection, trabecular resection, or iridectomy may cause hyphema (Fig. 36.2), blockage of aqueous outflow by blood clot, or vitreous hemorrhage. Some suggested surgical modifications to minimize these hemorrhagic complications in the anterior chamber include careful cauterization of bleeding vessels during flap dissection, dissecting the flap anteriorly into clear cornea so that trabecular resection occurs anterior to the scleral spur, and avoidance of iridectomy in patients with a high risk of hemorrhage.

Tube shunt procedures with mechanisms to reduce the extent of IOP reduction, i.e.,—valved tube shunts or tube ligature, may minimize the chances of a major hemorrhagic complication. Our systematic comparison of the flexible silicone plate Ahmed glaucoma valve vs. the hard polypropylene plate Ahmed glaucoma valve showed that the flexible silicone model was associated with a higher rate of complications. The higher rate of complications was possibly related to overfiltration and a lower IOP associated with the silicone plate Ahmed valve [16]. However, it must also be kept in mind that this study was a retrospective review and may not have adequate power to truly detect a difference. Knowing that low IOP is a risk factor for some of the serious complications of aqueous drainage devices, we suggest estimation of the IOP by digital palpation or actual measurement at the conclusion of silicone Ahmed glaucoma valve implantation. If the IOP is less than 8–10 mmHg, additional steps should be taken to avoid an occurrence of hypotony or a flat anterior chamber postoperatively. Additional steps may include, but are not limited to, injection of viscoelastic into the anterior chamber, tube ligature with an absorbable suture, and implantation of the device in two stages. It is our clinical experience that maintaining the IOP at mid to high 20's by filling the anterior chamber with viscoelastic material at the conclusion of surgery is required to avoid postoperative hypotony associated with silicone Ahmed glaucoma valve (model FP-7) [17].

Summary for the Clinician

- Acute reduction of high IOP is associated with a higher rate of hemorrhagic complications.
- Surgical modifications to minimize a sudden drop in IOP may be prudent.

References

1. Baudouin C, Liang H, Hamard P, et al. The ocular surface of glaucoma patients treated over the long term expresses inflammatory markers related to both T-helper and T-helper 2 pathways. Ophthalmology. 2008;115:109–15.
2. Korenfeld MS, Silverstein SM, Cooke DL, et al. Difluprednate ophthalmic emulsion 0.05% for postoperative inflammation and pain. J Cataract Refract Surg. 2009;35:26–34.
3. Jampel HD, Quigley HA, Kerrigan-Baumrind LA, The Glaucoma Surgical Outcomes Study Group, et al. Risk factors for late-onset infection following glaucoma filtration surgery. Arch Ophthalmol. 2001;119:1001–8.
4. Fiscella RG, Gaynes BI. Equivalence of generic and brand-name ophthalmic products. Am J Health Syst Pharm. 2001;58:616–7.
5. Levine MN. Risks and benefits of anticoagulant therapy. Semin Thromb Hemost. 1986;12:67–71.
6. Faxon DP, Nesto RW. Antiplatelet therapy in populations at high risk of atherothrombosis. J Natl Med Assoc. 2006;98:711–21.
7. Handin RI. Anticoagulant, fibrinolytic, and antiplatelet therapy. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's principles of internal medicine. 15th ed. New York: McGraw-Hill; 2001. p. 758–61.
8. Konstantatos A. Anticoagulation and cataract surgery: a review of the current literature. Anaesth Intensive Care. 2001;29:11–8.
9. Law SK, Song BJ, Yu F, Kurbanyan K, Yang TA, Caprioli J. Hemorrhagic complications from glaucoma surgery in patients on anticoagulation therapy or antiplatelet therapy. Am J Ophthalmol. 2008;145:736–46.
10. The Fluorouracil Filtering Surgery Study Group. Risk factors for suprachoroidal hemorrhage after filtering surgery. Am J Ophthalmol. 1992;113:501–7.
11. Dunn AS, Turpie AG. Perioperative management of patients receiving oral anticoagulants: a systematic review. Arch Intern Med. 2003;163:901–8.
12. Katz J, Feldman MA, Bass EB, Lubomski LH, Tielsch JM, Petty BG, Fleisher LA, Schein OD, Study of Medical Testing for Cataract Surgery Team. Risks and benefits of anticoagulant and antiplatelet medication use before cataract surgery. Ophthalmology. 2003;110:1784–8.
13. Jampel H. Glaucoma surgery in the patient undergoing anticoagulation. J Glaucoma. 1998;7:278–81.
14. Cobb CJ, Chakrabarti S, Chadha V, et al. The effect of aspirin and warfarin therapy in trabeculectomy. Eye (Lond). 2007;21:598–603.
15. Tuli SS, WuDunn D, Ciulla TA, et al. Delayed suprachoroidal hemorrhage after glaucoma filtration procedures. Ophthalmology. 2001;108:1808–11.
16. Law SK, Nguyen BS, Coleman AL, et al. Comparison of safety and efficacy between silicone and polypropylene Ahmed glaucoma valve in refractory glaucoma. Ophthalmology. 2005;112:1514–20.
17. Law SK, Kornmann HL, Giaconi JA, et al. Early aqueous suppressant therapy on hypertensive phase following glaucoma drainage device procedure: a randomized prospective trial. J Glaucoma. 2014 [Epub ahead of print].

Procedural Treatments: Bleb Needling

37

JoAnn A. Giaconi and Richard K. Lee

Core Messages

- Many different techniques exist for needle revision of filtering blebs.
- No randomized controlled trials comparing needle revision with other treatment modalities exist, so clinical decision-making is primarily based upon case series, reports, and personal anecdotes.
- Success rates of bleb needling vary with different definitions and time frames of success.
- Complications of bleb needling range from minor to sight-threatening.
- Deciding to needle is up to the individual surgeon, his/her experience, and comfort level with the procedure, bleb-associated factors, and the patient's ability to cooperate (especially for slit lamp needling).

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37.1 What Are the Different Techniques to Needle a Bleb?

Filtering blebs fail due to wound healing responses along the path of aqueous outflow (Fig. 37.1). There can be significant subconjunctival fibroblast proliferation and biosynthesis of collagen and other extracellular matrix materials in the area of trabeculectomy [1]. The concept behind bleb needling is to reestablish free flow of aqueous humor from the anterior chamber to the subconjunctival bleb space by cutting through postoperative scar tissue that prevents or decreases aqueous outflow. Needling cuts through adhesions formed between the conjunctiva and scleral flap and/or from scleral flap to scleral bed. A retrospective study of 119 trabeculectomies found that one-quarter of eyes underwent needling to increase the rate of filtering success [2]. As with any procedure, many variations exist with regard to bleb needling technique.

Prior to bleb needling, one needs to ascertain the source of reduced outflow. Slit lamp examination and gonioscopy are critical for determining alternative causes of blocked aqueous flow from the anterior chamber to the bleb that do not require needling for treatment. For example, the presence of iris plugging the sclerostomy may require anterior segment removal of the iris from the ostium with a cyclodialysis spatula and

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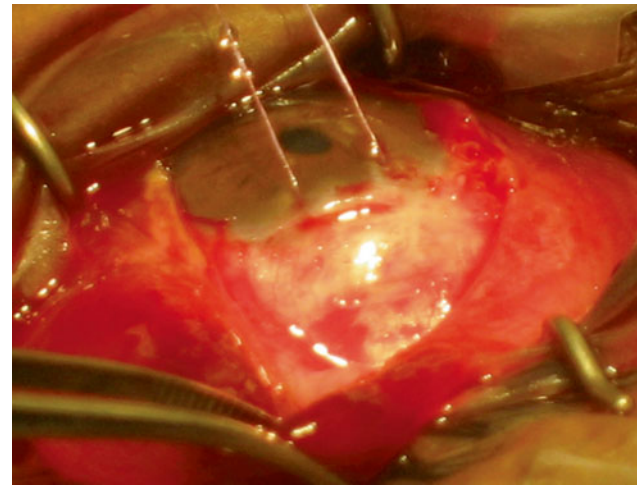

Fig. 37.1 An eye undergoing trabeculectomy revision for elevated IOP in the operating suite. After dissection of the conjunctiva and tenon's layer from the sclera, the previous trabeculectomy flap is not visible beneath the dense fibrovascular tissue that has formed, which blocks aqueous flow and led to failure of the initial MMC trabeculectomy

subsequent argon iridoplasty. Occasionally, a fibrinous membrane can form over the ostium that can be cut with the YAG laser to reestablish aqueous outflow.

If bleb needling is indicated, a variety of techniques described in the literature can be used. All needling procedures described use aseptic techniques (a few drops of povidone-iodine and/or antibiotic drops, or a full surgical prep) and anesthesia. The anesthesia options are topical anesthetic drops, lidocaine jelly, subconjunctival injection alone or mixed with antimetabolite, or a local orbital block.

Bleb needling can be performed in the clinic (which controls cost and is convenient) either at the slit lamp, with magnifying loupes, or at a microscope. Others perform bleb needling in the operating room, which allows for greater control of the eye and intravenous sedation of the patient. The apprehension of some patients upon hearing the words needling and eye used in the same sentence is not to be underestimated. Thus, careful patient selection is critically important for safe and effective bleb needling, especially at the slit lamp.

37.1.1 Slit Lamp Bleb Needling

Needling a bleb at the slit lamp requires careful preparation, especially if one is performing the procedure without assistance. Make sure the patient's bleb is easily accessible to a needle at the slit lamp while the patient looks downward and that the patient is able to maintain the requested head and eye positions. Also, assess the depth of the orbit and other anatomical features that may prevent optimal access to the bleb with a needle. If the patient's or physician's positioning is uncomfortable, the needling procedure is best performed in a procedure or operating room with the patient in a supine position.

Make sure to have all instruments, drops, medications, and anesthesia within easy reach. We normally apply several rounds of a fourth generation quinolone antibiotic, topical lidocaine, topical betadine, and then a povidone-iodine cleaning of the eyelid and eyelid margins before placement of a lid speculum at the slit lamp. Needles used vary from 30- to 24-gauge. Most surgeons use 25- or 27-gauge needles, which tend to be sturdier for cutting through scar tissue but are small enough not to leave a leaky conjunctival hole. Using the needle cap to bend the needle at its base to a 60° angle allows easier manipulation of the needle at the slit lamp (Fig 37.2). An MVR blade, usually used by retinal surgeons, may also be used.

The basic needling procedure is as follows, keeping in mind that this may sound relatively easy to do but can be quite a difficult procedure to execute successfully because of poor visualization, patient cooperation, and positional access to the bleb at the slit lamp. The needle is introduced

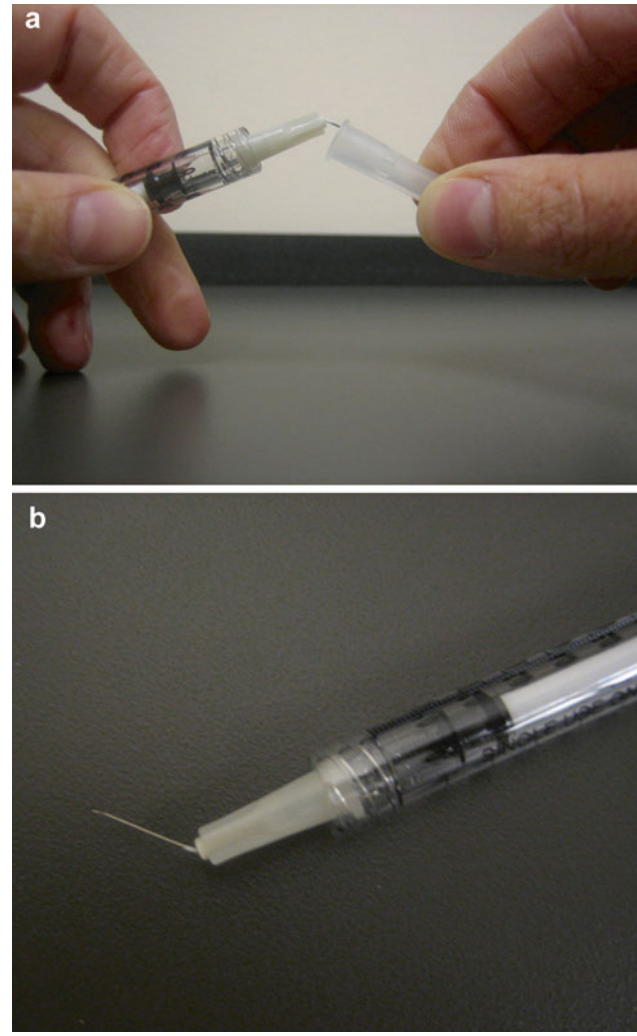

Fig. 37.2 (**a**, **b**) A 27-gauge needle is bent to approximately a 60° angle with the sterile needle cap in order to access the eye more easily at the slit lamp

into the subconjunctival space, generally 5–10 mm distal to the scleral flap area (Fig. 37.3), either superiorly or temporally (temporal is an easier approach if you are at the slit lamp). One does not want to enter the conjunctiva close to the scleral flap because of the risk of a persistent bleb leak close to the filtering site. The needle is advanced toward the area of intended revision and a to-and-fro movement is utilized to allow the cutting edges of the needle to move through scar tissue (bevel faces conjunctival side). If this is not successful in achieving a raised bleb, then attempts should be made to cut the sclera flap edges and lift the scleral flap with the needle. The needle can be advanced under the flap and through the trabeculectomy ostium until the needle tip is observed in the anterior chamber (Figs. 37.4 and 37.5). Observation of the needle tip in the anterior chamber demonstrates that a complete path has been established for aqueous outflow between the bleb and the anterior chamber. When the needle is inside the anterior chamber, vigilance must be maintained to keep the needle plane parallel to the iris so as not to hit the iris (to minimize the risk of bleeding and hyphema) or the lens (if the patient is phakic). A successful needling procedure will result in immediate bleb elevation as aqueous flow is reestablished. Care must always be taken not to tear the conjunctiva with the needle.

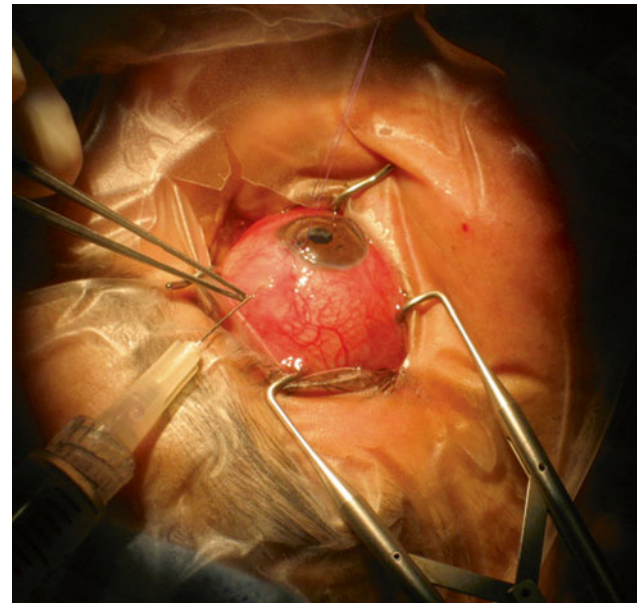

Fig. 37.3 A bleb revision in the operating suite. Notice that the needle entrance through the conjunctiva is located far from the limbus and the trabeculectomy flap in order to minimize aqueous leak after outflow is reestablished

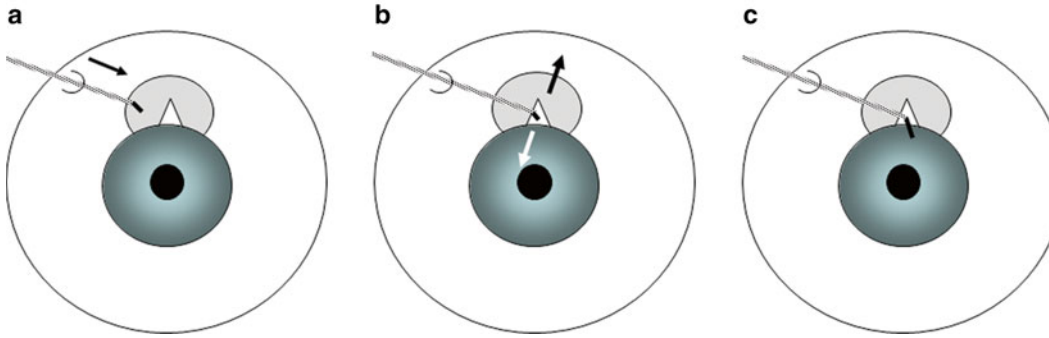

Fig. 37.4 Schematic drawing of bleb needling. (**a**) Needle entry into the conjunctiva should not be over or near the trabeculectomy flap. (**b**) The needle is advanced under conjunctiva toward the flap using a to-and-fro motion to cut adhesions. If this does not lead to outflow then, (**c**) the needle should be advanced underneath the trabeculectomy flap, again using a cutting movement, and into the anterior chamber to reestablish flow into the bleb. Figures courtesy of Palm Palmberg, M.D.

37.1.2 Bleb Needling in the Procedure or Operating Room

The technique in the operating room or in a procedure room is essentially identical to that at the slit lamp, except that the patient will be supine and the surgeon may feel that he/she has more control of the procedure. In the operating room, intravenous sedation can be given to the anxious patient. After appropriate anesthesia and sterile preparation of the eye, a corneal traction suture can be placed to infraduct the eye. This traction suture can improve visibility of the bleb and control eye position. Many variations exist as to how to proceed at this point.

37.1.3 Antimetabolite Use with Needling

Significant variation exists with regard to if, when, and how to use antimetabolites to prevent recurrent scarring. Some surgeons first needle

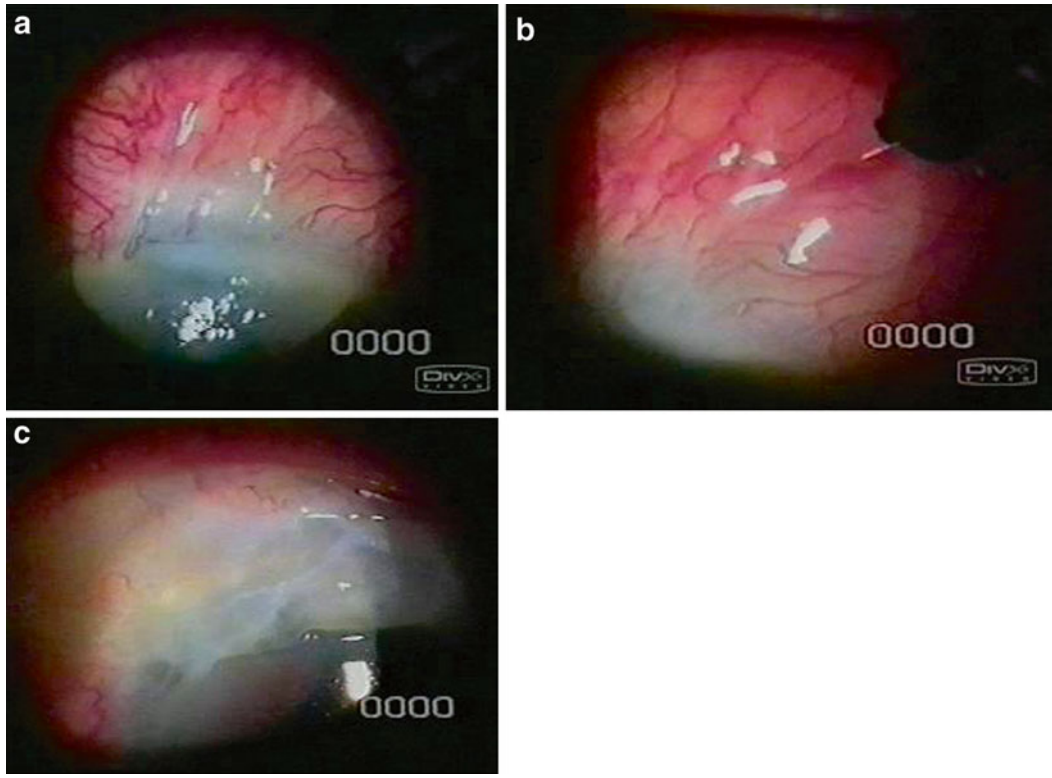

Fig. 37.5 Close-up photographs of bleb needling. (**a**) A flat, scarred bleb is seen initially with the needle bevel just under the conjunctiva. (**b**) The needle is moved to-and-fro to cut conjunctival adhesions and to get under the trabeculectomy flap, if necessary. (**c**) Months later, the same eye shows that a filtering bleb has evolved once again after a successful needling procedure. Photos courtesy Palm Palmberg, M.D.

and then inject antimetabolite at a site distal to the bleb revision site. Other surgeons will raise a subconjunctival bleb prior to needling, which helps dissect tissue and can make it safer to track the needle under conjunctiva. To raise a bleb, authors have described using balanced salt solution, local anesthetic with or without epinephrine, or a mixture of anesthetic and mitomycin-C in a 1:1 ratio (see Table 37.1).

Generally, 5-fluorouracil is used with slit lamp needling (it is injected after needling); 5 mg of 5-fluorouracil is administered, either 0.1 mL of 50 mg/mL or 0.2 ml of 25 mg/mL concentration. In the operating room, mitomycin-C is often used for needling, although some authors also use it at the slit lamp [3, 4]. Final concentrations of MMC injected vary up to 0.2 mg/mL. Some inject this mixture near the intended site of revision, while most direct it away from the site to minimize the chances of its entrance into the anterior chamber.

Table 37.1 Mitomycin-C concentrations and mixtures for bleb needling

MMC 0.02 mL (0.2 mg/mL) + 0.02 mL xylocaine with epi 2 % 0.02 mL [5]
MMC 0.1 mL (0.4 mg/mL) + 0.1 mL lidocaine 1 % nonpreserved [3]
MMC (0.004 mg/mL) + bupivacaine 0.75 % — total injected 0.03 mL, final concentration 0.13 mg/mL

An antimetabolite bleb, usually mixed with an equal amount of anesthetic, can be raised with a 30-gauge needle or with the gauge needle that will be used for needling. The subconjunctival fluid is then either massaged to spread it around or is left to sit in place. Generally, 5–30 min are allowed to pass prior to needling [3, 5–9].

Yet another variation is to apply MMC transconjunctivally. This technique is based upon the results of transconjunctival MMC application during filtering surgery in rabbits. The authors of this technique prefer an operating room setting.

They perform the needling procedure and then close the conjunctival entrance wound with an 8-0 vicryl suture. A Weck-cel sponge soaked in MMC 0.5 mg/mL is held in contact with conjunctiva in the area of elevated bleb for 6 min, followed by a balanced salt solution rinse and 0.5 mL injection of betamethasone [10]. Postoperatively, the eye is treated with antibiotics and steroids for a number of weeks.

The use of MMC and 5-FU can be complicated by endothelial cell loss if MMC enters the anterior chamber or by corneal epithelial defects if 5-FU touches the epithelium. Some surgeons tint the antimetabolite injection with Trypan blue in order to visually assess whether or not MMC or 5-FU enters the anterior chamber or leaks onto the corneal surface [11].

At the end of needling, one should administer topical antibiotic and give patients instructions on their postoperative use. The intraocular pressure (IOP) should be remeasured to gauge the success of the procedure. The signs and symptoms of endophthalmitis should also be reviewed.

Summary for the Clinician

- Different techniques of needling with or without antimetabolites can be used, but common to all procedures are aseptic techniques, some form of anesthetic, and postoperative antibiotics and steroids.
- If 5-FU is used, inject 5 mg (0.1 mL of 50 mg/mL or 0.2 mL or 25 mg/mL).
- MMC can be used in various concentrations (up to 0.2 mg/mL).
- Needling can be performed first, followed by injection of antimetabolite.
- Ballooning of the conjunctiva can be performed first with balanced salt solution, anesthetic, or a mixture of anesthetic plus MMC, followed by needling.
- Needles from 30- to 24-gauge may be employed, but 25- and 27-gauge are most commonly utilized.
- Needling can be performed with the patient sitting at the slit lamp or supine with an operating microscope.

37.2 Is It Ever Too Early or Too Late to Needle a Bleb?

Failing blebs can be needled at any time. Needling has been performed as early as the first postoperative week [6] and as late as 31 years after the initial trabeculectomy [12]. In the first few weeks following trabeculectomy, if the IOP is higher than the target pressure, options to lower the pressure include digital ocular pressure, laser suture lysis, and removal of releasable sutures. If a bleb continues to fail after conservative measures, options include restarting IOP-lowering medications, bleb needle revision, or reoperation to revise the trabeculectomy.

A number of studies indicate that the interval between initial filtering surgery and bleb needling appears to make no difference with regard to outcomes [6, 8, 13, 14]. One study found that the results of MMC needling were better if performed within 4 months of trabeculectomy. The trabeculectomies in this study were performed *without* antimetabolite, so the results suggest that earlier modulation of wound healing with antimetabolite is possibly better than late modulation [15].

Reported risk factors for needling failure are higher preneedling pressures (>30 mmHg), lack of MMC use during initial surgery, and IOP >10 mmHg immediately after needling [6, 9, 16]. The type of bleb being needled does not appear to affect the outcome, per statistical analyses in multiple case series of no more than 100 eyes, although some authors believe that the best success occurs when there is a bleb present preneedling [17] and in those blebs that are cystic, cystic in part, or diffuse [6].

Needling can also be performed on encapsulated blebs. Encapsulated blebs usually occur in the early postoperative period and are tense, smooth, dome-shaped cysts of aqueous with a thick wall. A Cochrane review of the literature was performed on this topic and only one prospective study was identified that randomized 25 eyes to needling without antimetabolite or medical management. No difference was found between the two treatment options [18]. Encapsulated blebs often do well with topical

medication treatment over several months to allow thinning of the bleb. If this fails, then surgical revision or another glaucoma filtering procedure can be performed.

Summary for the Clinician

- Failing blebs have been needled within a week to decades after initial trabeculectomy.
- The interval between needling and trabeculectomy may not be a risk factor for failure of the procedure.
- Achieving a low IOP (≤10 mmHg) immediately after needling has an effect on long-term success.
- Needling may be more successful on partially functioning blebs than on completely nonfunctional blebs.
- Needling an encapsulated bleb has not been shown to be more successful than medical treatment.

37.3 Are There Any Limits on How Often I Can Perform Needling and Injection of Antimetabolite? Should Antimetabolite Always Be Injected with Needling Procedures?

In many reports, multiple needlings are needed to achieve success. This may reflect the fact that the initial needling did not reestablish flow. Greenfield et al. reported that success was more likely after one needling procedure rather than after multiple needlings [8]. After 2–4 attempts, many surgeons will conclude that needling is not beneficial for the individual eye and consider surgical revision. Theoretically, a risk of scleral melt can occur with increasing exposure to antimetabolites. Multiple needlings using antimetabolite after MMC trabeculectomy can lead to friable sclera with loss of scleral integrity leading to a more difficult surgical revision.

No randomized prospective clinical trial to determine the benefit of adjunctive 5-FU or MMC during needling procedures has been published, possibly because many clinicians using these antimetabolites believe its use to be justified on clinical experience and anti-fibrosis theory [6]. It is generally believed that needling with adjunctive antimetabolites is a more successful procedure than needling alone. Of note, definitions of success vary in the literature. Most case series use a rather lax definition of success: IOP <21 or 22 mmHg with or without medications. Additionally, the postoperative periods reported vary so that direct comparison of study results is difficult.

Summary for the Clinician

- Often, more than one needling is attempted in order to successfully lyse adhesions blocking aqueous flow; however, if the first needling attempt does not succeed it probably becomes less likely that subsequent attempts will succeed.
- Surgical revision should be considered if several needling attempts have failed.
- Needling with antimetabolite is considered more successful than needling without antimetabolite.

37.4 What Complications Should I Anticipate After Needling?

Following needling procedures, one may encounter bleb leaks, hyphema, corneal epithelial 5-FU toxicity (epithelial defects), bullous keratopathy, hypotony, shallow or flat anterior chambers, serous choroidal detachment,

suprachoroidal hemorrhage, malignant glaucoma, blebitis, and endophthalmitis. These complications can be painful, chronic, and/or vision-threatening, and patients should give informed consent before performing the procedure. Risk-minimizing procedures, such as the use of antibiotics and antiseptics prior to needling and the use of topical antibiotics after needling, should be used. Patients who are on aspirin or other anticoagulants should be warned about the increased risk for bleeding (or anticoagulation can be stopped prior to the procedure if not medically contraindicated) and additional care should be taken needling around blood vessels. Management of complications will be similar to the management of complications after primary trabeculectomy.

Summary for the Clinician

- Complications are possible following needling and they resemble complications seen after trabeculectomy.
- Complications unique to needling are bleb leaks at the needle entrance wound, and iris or lens damage from needle entrance through the sclerostomy.

37.5 Is It Better to Needle or Reoperate on a Failing Bleb?

Pose this question to different glaucoma specialists and one will receive different answers. No consensus exists, as there is no high-quality evidence in the form of randomized, controlled trials comparing needling to revision of failing blebs. Some surgeons find their outcomes with needling to be acceptable and the procedure to be convenient; others find the outcomes less than desirable while putting patients at risk for complications and so they rarely perform the procedure.

The literature reports varying rates of success. It is difficult to make inter-study comparisons when different studies use different definitions of success and different methods (i.e. different number of needlings, different antimetabolite, different technique, different initial trabeculectomy procedure, etc.). Table 37.2 summarizes some of the relevant literature. Overall, needling appears to be "successful" in about one-third of patients. Success drops off with longer follow-up. Whether to needle or not is up to the individual surgeon and the clinical presentation of the failing bleb. The success rate of reoperating on a failed trabeculectomy is also difficult to obtain and may not be remarkably higher than needling by the

Table 37.2 Summary of literature on bleb-needing results

Study author and definition of success	Success without medications (%)	Qualified success with or without medications (%)	Kaplan-Meier survival
Gutiérrez-Ortiz [15], ≤21 mmHg	44.1	85.3	90 % at 1 year
			75 % at 2 years
Broadway [6], <22 mmHg with no meds or less therapy than before	59.4	NA	75 % at 1 year
			52 % at 3 years
Rotchford [9], >20 % drop or ≤21 mmHg	NR	NR	54.3 % at 1 year
			45.7 % at 2 years
			31.9 % at 3 years
Fagerli [5], ≤18 mmHg	44.2	88.5	NR
Shetty [3], 4–21 mmHg	39	64	NR
Jacobs [7], <18 mmHg	39	68	NR
Greenfield [8], ≤22 mmHg	NR	73	NR

NA not applicable, *NR* not reported

experienced ophthalmologist. In one study, the Kaplan-Meier survival for maintaining IOP between 5 and 18 mmHg and at least a 20 % decrease in IOP after surgical revision was 38 % at 3 years without any intervening medication or needling [19].

Summary for the Clinician

- Needling has relatively low success rates, but probably not significantly lower than surgical revision of the bleb.
- Benefits of needling include the convenience of performing the procedure in the clinic, low cost, and potentially shorter recovery time for the patient.
- Needling can be successful in some patients—it can reduce IOP and reduce need for medications or surgery.
- The downsides of needling are that it is not predictable, requires technical skill, and can be difficult to perform (especially at the slit lamp).

References

1. Skuta GL, Parrish RK. Wound healing in glaucoma filtering surgery. Surv Ophthalmol. 1987;32:149–70.
2. King AJ, Rotchford AP, Alwitry A, et al. Frequency of bleb manipulations after trabeculectomy surgery. Br J Ophthalmol. 2007;91:873–7.
3. Shetty RK, Wartluft L, Moster MR. Slit-lamp needle revision of failed filtering bleb using high-dose mitomycin C. J Glaucoma. 2005;14:52–6.
4. Mardelli PG, Lederer Jr CM, Murray PL, et al. Slit lamp revision of failed filtering blebs using mitomycin C. Ophthalmology. 1996;103:1946–55.
5. Fagerli M, Løfors KT, Elsås T. Needling revision of failed filtering blebs after trabeculectomy: a retrospective study. Acta Ophthalmol Scand. 2003;81:577–82.
6. Broadway DC, Bloom PA, Bunce C, et al. Needle revision of failing and failed trabeculectomy blebs with adjunctive 5-fluorouracil: survival analysis. Ophthalmology. 2004;111:665–73.
7. Jacobs S, Gillis A, Van Malderen T, et al. Needling-revision of failed filtering blebs. Bull Soc Belge Ophtalmol. 2005;297:59–64.
8. Greenfield DS, Miller MP, Suner IJ, et al. Needle elevation of the scleral flap for failing filtering blebs after trabeculectomy with mitomycin C. Am J Ophthalmol. 1996;122:195–204.
9. Rotchford AP, King AJ. Needling revision of trabeculectomies bleb morphology and long-term survival. Ophthalmology. 2008;115:1148–53.
10. Iwach AG, Delgado MF, Novack GD, et al. Transconjunctival mitomycin-C in needle revisions of failing filtering blebs. Ophthalmology. 2003;110:734–42.
11. Franks W. Trypan blue staining of antiproliferative agents for trabeculectomy surgery and bleb needling. Br J Ophthalmol. 2005;89:1394–5.
12. Ung CT, Von Lany H, Claridge KG. Late bleb needling. Br J Ophthalmol. 2003;87(11):1430–1.
13. Cohen JS, Shaffer RN, Hetherington J, Hoskins D. Revision of filtration surgery. Arch Ophthalmol. 1977;95:1612–5.
14. Ewing RH, Stamper RL. Needle revision with and without 5-fluorouracil for the treatment of failed filtering blebs. Am J Ophthalmol. 1990;110:254–9.
15. Gutierrez-Ortiz C, Cabarga C, Teus MA. Prospective evaluation of preoperative factors associated with successful mitomycin C needling of failed filtration blebs. J Glaucoma. 2006;15:98–102.
16. Shin DH, Kim YY, Ginde SY, et al. Risk factors for failure of 5-fluorouracil needling revision for failed conjunctival filtration blebs. Am J Ophthalmol. 2001;132:875–80.
17. Kapetansky FM, Kapetansky SD. Antimetabolite use in revising failing filtering blebs. Semin Ophthalmol. 1999;14:144–51.
18. Feyi-Waboso A, Ejere HOD. Needling for encapsulated trabeculectomy filtering blebs. Cochrane Database Syst Rev. 2004;1, CD002658.
19. Anand N, Arora S. Surgical revision of failed filtration surgery with mitomycin C augmentation. J Glaucoma. 2007;16:456–61.

Procedural Treatments: Glaucoma Drainage Devices

38

David Dueker, Carson Bee, and Jim Robinson

Core Messages

- There are unique operative and postoperative differences between valved and nonvalved glaucoma drainage devices.
- There are surgical tips for glaucoma drainage device implantation when there is poor conjunctiva, aphakia, or significant peripheral anterior synechiae.

38.1 Is One Tube Shunt Design Better Than Another at Lowering IOP?

No one shunt has become the predominant choice of glaucoma surgeons for lowering IOP, yet. The reason for this may be that there is no clearly superior design with regards to IOP, or that there is a superior design but the available evidence does not reveal this fact, or that factors other than IOP lowering ability influence a surgeons' selection of device.

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There are two ongoing randomized clinical trials—the Ahmed Baerveldt comparison (ABC) study and the Ahmed versus Baerveldt (AVB) study—comparing two devices currently in widespread use [1, 2], a valved implant (Ahmed, 185 mm^2) and a larger nonvalved device (Baerveldt, 350 mm^2). Five-year outcomes from the ABC study, and 3-year treatment outcomes from the AVB study have been published, with final 5-year AVB results soon to follow. Both studies have demonstrated similar efficacy of the two implants in reducing IOP, with the ABC concluding that a greater IOP reduction was achieved with the Baerveldt Glaucoma Implant.

At 5 years in the ABC study, average pressure in the Ahmed Glaucoma Valve (AGV) group was 14.7 ± 4.4 mmHg, while average pressure in the Baerveldt group was 12.7 ± 4.5 mmHg ($p = 0.015$). With slightly different inclusion criteria, average pressure in the AVB study at 3 years with the Ahmed valve was 15.7 ± 4.8 mmHg and average pressure with the Baerveldt implant was 14.4 ± 5.1 mmHg ($p = 0.09$). Both studies demonstrated a lower postoperative IOP in the Baerveldt groups, although this difference was significant only at 5 years in the case of the ABC study, and not significant at both the 1 and 3 year intervals in both studies.

In addition, other interesting trends have emerged. The Ahmed valve groups in both studies have required more postoperative glaucoma medications, while the Baerveldt implant groups have experienced more episodes of hypotony and

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other serious postoperative complications. In the ABC study, the Baerveldt group was more likely to fail because of safety issues while the Ahmed group was more likely to fail because of inadequate IOP control. Despite these differences, similar cumulative rates of overall failure (21–44.7 %) were observed in both studies when a postoperative IOP target of 21 mmHg was used.

Further results from these trials should provide a more definite answer to this question and may clarify other features that should be considered in selecting a device for a given patient. The 5-year results from the ABC study may indicate that the larger, nonvalved Baerveldt implant may be preferred for patients in whom the lowest possible postoperative IOP is the primary goal. However, the apparent 2 mmHg advantage in IOP control must be weighed against the higher relative risk of safety related failures. At the time of this writing, a detailed account of ABC study complications is forthcoming.

Summary for the Clinician

- There is evidence to support the statement that the Baerveldt Implant may lower pressure slightly more than the Ahmed Valve for long-term IOP control.
- There is evidence to support the statement that the Baerveldt Implant is associated with more vision threatening complications than the Ahmed Valve.
- The choice of glaucoma drainage implant must be a balanced consideration of risks and benefits to the individual patient.

38.2 How Do Tube Shunts Lower IOP?

In the history of shunt development, there is evidence that a shunt made from tubing alone (as in the case of the original Krupin-Denver Valve design [3]) ultimately has limited effect once fibrotic encapsulation occurs around the tube's subconjunctival end. Molteno improved the long-term success of these devices by adding a plastic plate at the end of the tube [4]. Fibrosis still occurred around the implant, but now the surface area of the fibrotic encapsulation was greatly enlarged and allowed increased surface area for passage of fluid.

All devices currently on the market include a plastic plate at the distal end of the tube to establish such an enlarged space for aqueous humor drainage. Given that a larger surface area for drainage improved the general performance of early devices, it is reasonable to suppose that the size of the plate would correlate with the final pressure; that is, under comparable conditions, a device with a larger plate should result in a lower IOP than one with a smaller plate. In fact, when devices with different surface areas have been compared, final IOP is generally lower with a larger plate size [5]. However, there may be an upper limit to the advantage of a larger plate. A comparison of the largest Baerveldt Implant (500 mm^2) to the mid-size Baerveldt Implant (350 mm^2) [6, 7] showed similar final IOP levels yet better clinical outcomes overall with the 350 mm^2 implant. Currently, available implant surface areas range from approximately 100–350 mm^2 (see Table 38.1). The physical shape and chemical composition of the plate itself may also be important determinants of long-term success.

In addition to plate size, long-term IOP control is influenced by tissue response to the implant, i.e., the thickness and porosity of the capsule that forms around the implant's plate [8]. One hypothesis proposes that the capsule may evolve to allow more outflow ultimately if the early postoperative aqueous humor does not reach the tissue forming around the plate [9]. If this hypothesis is proven true, two-stage procedures and perhaps ligature with anterior venting slits may be preferable to valved devices that allow substantial immediate flow of aqueous around the plate. In the ABC study mentioned above, for example, a valved implant (Ahmed, 185 mm^2) is compared to a larger nonvalved device (Baerveldt, 350 mm^2). The study results,

Table 38.1 Currently manufactured glaucoma drainage devices

Device and manufacturer	Smallest plate surface area (mm^2)	Largest plate surface area (mm^2)	Valved vs. nonvalved
Ahmed devices (New World Medical, Rancho Cucamonga, CA)	96 (pediatric model)	364 (Double plate model)	Valved
Baerveldt implants (Advanced Medical Optics, Santa Ana, CA)	250	350	Nonvalved
Krupin implant (E. Benson Hood Labs, Inc., Pembroke, MA)		180 (Only available model)	Valved
The Molteno implants (Molteno Ophthalmic Ltd, Dunedin, New Zealand)	133	265 (Double plate)	Nonvalved

however, do not tell us why the Baerveldt results in slightly lower pressures on average—is it due to the larger plate size or due to the fact that the capsule is allowed to develop without exposure to early postoperative aqueous humor? The tissue around the plate provides passive flow resistance somewhat analogous to the wall of a trabeculectomy bleb, and that apparent similarity has led several investigators to apply antifibrotic agents to adjacent tissue during implantation of a drainage device. However, the bulk of evidence suggests that applying mitomycin C to the tissues adjacent to an aqueous shunt does not offer clear benefit [10].

Valved and nonvalved shunts have different postoperative IOP courses. Early pressure control is primarily determined by restricted or unrestricted flow. Tube size plays little role in pressure control: all of these devices use tubes with a 300 μm inner diameter, which provides no meaningful resistance to aqueous flow. Early pressure control is more reliable in devices with built-in flow control that are designed to avoid early postoperative hypotony (although hypotony still occurs occasionally). In nonvalved implants, early flow is either nonexistent (for example, in a two-stage surgery or when the tubing is fully occluded temporarily) or dependent on the surgeon producing exacting modifications of the small silicone tube. When there is no built-in flow control mechanism (Baerveldt and most Molteno models), different strategies have been employed to prevent excessive flow and hypotony in the early postoperative period. In one effective albeit complicated approach, the surgery is performed in two stages. In the first operation of a two-stage procedure, the device's plate is sewn into place, but the tube is not inserted into the eye. After allowing some time for healing to produce a fibrotic capsule around the plate (usually 6–8 weeks), a second operation is performed to insert the tube into the eye. At this point in time, the fibrous capsule around the plate provides sufficient resistance in most cases to prevent over-filtration and hypotony. Alternatively (to avoid a second surgical session), the tube of a nonvalved implant may be placed in the eye at the initial operation, but the flow is blocked in some manner to avoid hypotony. Flow is usually blocked by ligation with a releasable suture. Many surgeons also create small slits in the tube, proximal to the ligature, to allow a small degree of aqueous egress and thus some early pressure control prior to ligature release. The ligature itself may be self-releasing (e.g., 7-0 vicryl tightly tied around the tube) (Fig. 38.1) or may be released directly by the surgeon by various means (Figs. 38.2, 38.3, and 38.4).

Summary for the Clinician

- Some studies using Baerveldt and Molteno tubes show that larger surface plate area leads to better pressure control.

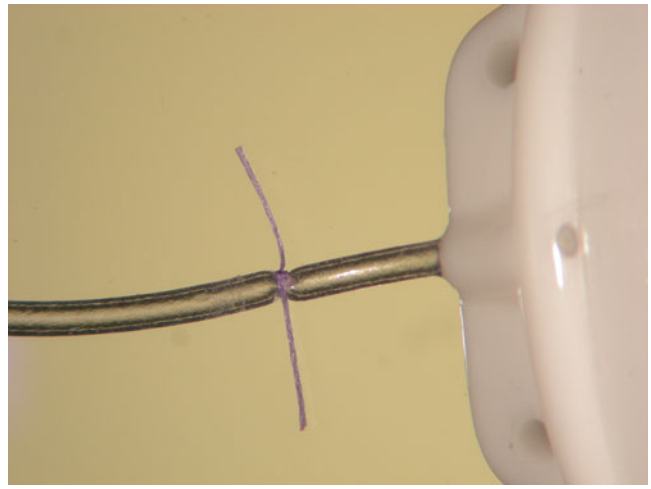

Fig. 38.1 To avoid excessive flow and consequent hypotony, the tube on a nonvalved implant (Baerveldt 350 mm^2 shown here) is occluded by various means—in this case by a braided 7-0 or 8-0 vicryl suture tied around the tubing to close the lumen. It is important to confirm complete occlusion by perfusing with balanced salt solution. This type of occlusion will usually self-release after approximately 6 weeks. If the suture does not spontaneously release, it is sometimes possible to loosen the suture with transconjunctival laser application (similar to laser suture lysis after trabeculectomy) or with a sharp needle (in the manner of bleb needling). Some surgeons provide a degree of early filtration by carefully incising the tubing with a super sharp blade or piercing it with a spatulated needle to provide drainage slits (1 mm or less) running parallel to the tubing [18]

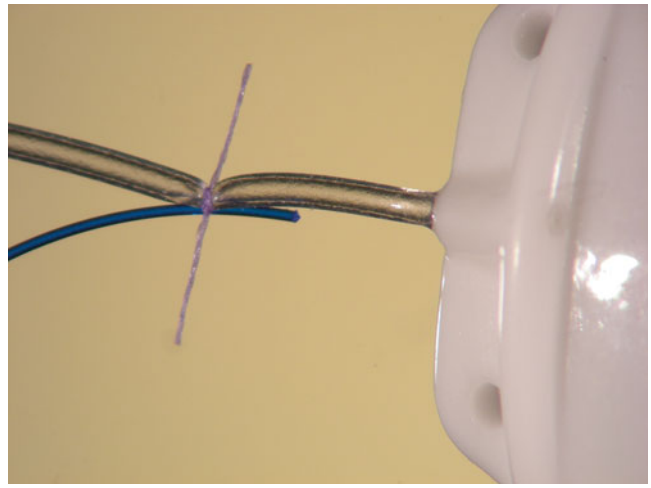

Fig. 38.2 An external "ripchord" technique where the tube is occluded by a tightly tied braided 7-0 or 8-0 vicryl suture which encompasses both the tubing and one end of a piece of 4-0 prolene suture. The other end of the prolene suture is placed in an inferior subconjunctival pocket created by blunt dissection. To release the occlusion at the surgeon's discretion, the inferior end of the prolene ripchord is exposed (using topical anesthesia and a small scissors), the exposed end is grasped with forceps, and the prolene removed completely—thus providing space for the tubing to expand and allowing fluid to pass. The plate is anchored to the globe in the usual fashion; in addition, a mattress suture (7-0 or 8-0 vicryl) is placed to anchor the tubing to the sclera on either side of the occlusion for stability during removal of the ripchord. If the ripchord is not pulled, the prolene may simply be left in place and the tubing will open spontaneously when the encircling vicryl suture dissolves [19]

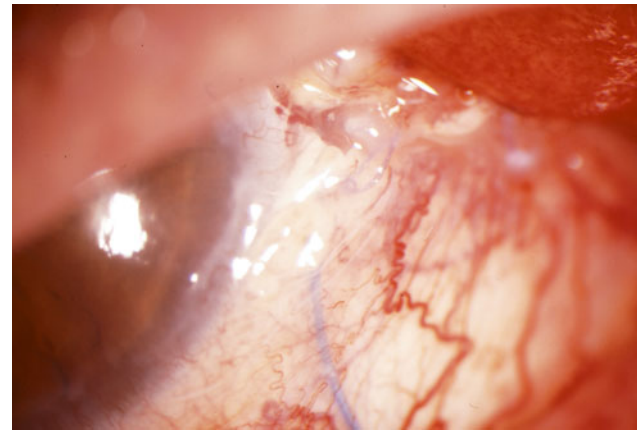

Fig. 38.3 A 4-0 prolene ripchord suture extends under the conjunctiva, and can be removed as described in the legend for Fig. 38.2. Photo courtesy of Joe Beringer

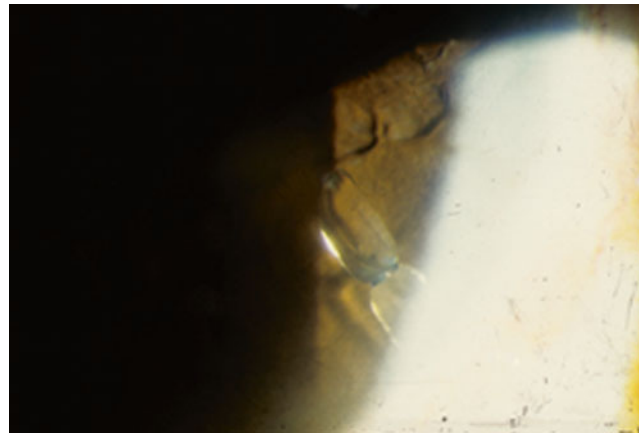

Fig. 38.4 An alternative method for temporary tube occlusion uses a 9-0 or 10-0 prolene "tourniquet suture" (some surgeons use nylon) to tie off the tube near its tip prior to inserting it into the anterior chamber. Flow through the tube can be initiated by applying laser energy to the suture to order to melt and loosen it, which will allow the lumen to open. Typical argon laser settings: power 200–300 mW, duration 0.1–0.2 s, spot size 50–100 μm [20]

- The fibrous capsule that forms around the plate probably affects IOP control—a more porous capsule will allow more flow and a dense capsule will allow less flow.
- In one hypothesis, early capsule exposure to inflammatory postoperative aqueous may be a factor that leads to less efficient aqueous drainage.

38.3 Are There Certain Circumstances/Diagnoses Where One Type of Shunt May Be Preferred over Another?

Initially, tube shunts were used in eyes with limited visual potential, often in cases where trabeculectomy had already failed, or where trabeculectomy was considered unlikely to

succeed (e.g., excess conjunctival scarring). As tube shunts have proven their effectiveness and have shown reduced complication rates (in some ways) compared to traditional filtering surgery, they are being considered more and more as an initial surgical intervention for many types of glaucoma. This expanded use has meant that an increasing number of eyes undergoing this surgery may have better vision and visual potential than the original target population for tube shunt use. Despite this increasing experience with tube shunts, currently there is very little evidence that one tube shunt is the best choice for a given diagnosis. However, it is possible to offer some guidelines that may be useful in selecting one implant over another.

For the beginning tube shunt surgeon, a device with built-in flow restriction is a reasonable choice. Early pressure control is generally good with these devices, and there is no need to select and personally handcraft a means of flow restriction during surgery. Early reliable pressure control definitely simplifies the postoperative care. Also, for the beginning or occasional implant surgeon, use of a smaller single plate device simplifies the surgery by restricting surgery to one quadrant and eliminating the need to maneuver the implant around the rectus muscles.

Even for the surgeon experienced in modifying a nonvalved implant to allow some early flow, a valved implant may be preferred when very reliable pressure control is critical in the early postoperative period. A valved implant is also a good choice when circumstances may not allow reliable scheduling of postoperative visits. Finally, a valved implant may be preferred in a patient at high risk for choroidal hemorrhage (high blood pressure, initial very high intraocular pressure, use of anticoagulants). Early release of a tube ligature or even release at the anticipated interval—approximately 6 weeks—with a slowly healing fibrous capsule may allow for a sudden drop in pressure, placing the eye at risk for choroidal hemorrhage. Built-in flow control should make such dramatic changes in intraocular pressure less likely. However, it must be acknowledged: "At present, there are insufficient published data to draw any definitive conclusions about the relative likelihood of early postoperative hypotony with implantation of valved or nonvalved devices [10]."

When ultimate pressure must be very low, there is evidence that increased plate size should be considered (as discussed in Sect. 38.2). In such cases, conjunctival scarring or other tissue changes may determine whether it is better to use a large single plate or a double plate device.

Summary for the Clinician

- Valved devices provide more reliable pressures in the early postoperative period, which may be advantageous in patients where early postoperative pressure decrease is critical or where there are many risk factors for choroidal hemorrhage.
- Beginning tube shunt surgeons may feel more comfortable with valved devices and devices with smaller plates.

38.4 What Kind of IOP Results Can I Expect with a Tube Implant?

Early experience with tube shunt devices provides information about IOP results, but it is difficult to provide generalizable estimates from these studies. These early studies included a variety of complicated, refractive glaucomas of varying cause, and failure rates were often high, with the highest rates being reported in neovascular glaucoma.

Better estimates of expected IOP results are now available from studies in which less complicated glaucoma has been treated in randomized comparison of trabeculectomy vs. a tube shunt. In a prospective study comparing the Ahmed valve (S-2 model) with trabeculectomy, good pressure outcomes were found in both arms, with final mean pressure at 1 year being lower in the trabeculectomy arm. Average pressure with trabeculectomy was

11.4 mmHg, while average pressure with Ahmed valve was 17.2 mmHg ($p=0.01$). The Ahmed valve group required more postoperative glaucoma medications [11]. With longer follow-up (3–5 years), intraocular pressures between the groups were not significantly different (13.6 mmHg, trabeculectomy vs. 13.1 mmHg, Ahmed) [12].

In the Trabeculectomy vs. Tube (TVT) Study, a Baerveldt implant (350 mm^2) was compared to mitomycin-C trabeculectomy. Intraocular pressure results were generally good in both groups, with slightly lower pressure in the trabeculectomy group. The average pressure at 5 years was 12.6 ± 5.9 mmHg in the trabeculectomy group and 14.4 ± 6.9 mmHg in the Baerveldt group, which was not significantly different ($p=0.12$). Postoperative medication requirement was not significantly different at 5 years. Cumulative probability of failure at 5 years was higher in the trabeculectomy group (46.9 % vs. 29.8 %, $p=0.002$), as well as the need for additional glaucoma surgery (29 % vs. 9 %, $p=0.025$) [13].

Summary for the Clinician

- IOP results comparable to trabeculectomy can be achieved with tube shunt surgery in less complicated glaucomas.
- Higher rates of failure and additional glaucoma surgery are generally seen after trabeculectomy than after tube shunts at 5 years.

38.5 What Are the Differences in Postoperative Course Between a Valved and Nonvalved Tube Shunt?

Valved implants allow aqueous to immediately flow to the plate. Their flow-restricting mechanisms theoretically keep IOP between 8 and 18 mmHg in the immediate postoperative period, and therefore there is immediate IOP control. Early supplemental medications are generally unnecessary, which can make the early postoperative instructions to the patient simpler (only topical antibiotic and steroid are necessary typically). A hypertensive phase can develop anywhere between 4 and 16 weeks after implantation, in which IOP may jump into the high 20s or 30s [14]. The etiology of the hypertensive phase is believed to be fibrous capsule remodeling into a denser, less porous structure. It is thought that early exposure to aqueous filled with inflammatory cells and mediators (such as VEGF in the case of neovascular glaucoma) causes remodeling. Postoperative follow-up must be scheduled in anticipation of this possible development to avoid prolonged periods of exposure to high pressure. Some surgeons prescribe aqueous suppressants while the IOP is still low, in the hope of preventing a hypertensive phase.

With nonvalved shunts, immediate postoperative IOP can be more variable and depends on the procedure of implantation chosen. If a two-stage procedure is performed and the tube is not placed into the anterior chamber, all preoperative medications must be continued until the second operation. Because the development of the fibrous capsule is not predictable in all cases, there can be cases of hypotony after the tube is placed into the anterior chamber. If the tube is ligated and venting slits are placed, again the IOP may be unpredictable; the venting slits may be variable in their flow and some aqueous may reach the plate. Once the ligature opens, either spontaneously (Fig. 38.1) or by surgical intervention (in the case of a rip chord (Fig. 38.2)), and if the capsule is not ideally formed, the IOP can suddenly drop, exposing the eye to the risk of late hypotony and late choroidal hemorrhage. Patients should be seen weekly starting around 5–6 weeks in anticipation of the ligature opening so that glaucoma medications can be discontinued as needed. The opening of the ligature can also be accompanied by significant inflammation, which should be managed on a case-by-case basis.

Summary for the Clinician

- Careful early postoperative care is needed for all implants to monitor and treat either a hypertensive phase or hypotony and to manage inflammation.

38.6 What Can I Do if the Conjunctiva Will Not Close and Cover the Tube Shunt as I Am Finishing the Surgery?

Of course the tube shunt itself must be fully covered at the end of surgery. The scleral portion of the tube should be covered first by a protective graft and then the graft itself is covered by the conjunctiva and Tenon's layer. It is this final closure of conjunctiva over the graft material that can sometimes be challenging.

As with many problems, often this dilemma can be anticipated and avoided by careful preoperative examination and planning. Preoperative assessment should include evaluation of the anticipated implantation site (most often the supero-temporal quadrant). If the conjunctiva is thin, immobile, scarred, or atrophic, an alternative site should be considered and evaluated. Usually the alternative will be an inferior quadrant, with some advocating infero-nasal over infero-temporal placement. If the anterior conjunctiva is severely scarred in all potential quadrants, it may still be possible to implant a tube more posteriorly through the pars plana. This requires a very careful and complete vitrectomy to avoid vitreous blocking the tube and may not be an option in all cases.

Despite careful preoperative examination and selection of the surgical site, the surgeon still may be confronted with a problem closing conjunctiva. Usually this results from the conjunctiva being inelastic and not stretching adequately to cover the extra bulk of the implant and overlying protective graft. Additional careful dissection underneath the conjunctiva/Tenon flap should be tried to lyse any remaining attachments to adjacent tissue, thus allowing the tissue freer forward movement. If this does not help, it is possible that the conjunctiva is more constricted than the underlying Tenon's fascia. In that case, incising conjunctiva only, in peritomy fashion posteriorly, will often allow the anterior conjunctiva to slide forward and cover the graft. A bare patch of exposed Tenon's fascia will remain posteriorly, but this will readily epithelialize.

If all these maneuvers still leave a small strip of exposed graft (1 mm or less) at the limbus, one of us (JCR) has found that this small gap will almost always eventually epithelialize with adjacent conjunctiva. If a larger area remains exposed, a free graft of conjunctiva can be harvested from another quadrant and sewn in to cover the graft.

In the very rare circumstance where the conjunctiva is so fragile that it breaks down with normal handling and will not hold a suture, it may be necessary to abandon the surgical site and move to a different quadrant.

Summary for the clinician

- Careful preoperative evaluation of conjunctival scarring is important and alternative quadrants or pars plana placement should be considered for implant placement.
- Options if conjunctiva does not reach the limbus at the end of the case:
  - Additional dissection to catch missed adhesions.
  - Separating conjunctiva from Tenon's layer and then creating a posterior peritomy in the conjunctiva so that it slides forward separately from Tenon's layer. The posterior gap will epithelialize.
  - Leave a gap that is <1 mm in width to epithelialize.
  - Consider abandoning the surgical quadrant and move to another site.

38.7 What Patch Graft Materials Should I Use?

In the past, glaucoma drainage implant tubes have been inserted into the anterior chamber under a partial thickness scleral flap, created by the surgeon specifically for this purpose. This is a technically challenging technique with a high risk of complications, especially in eyes that have already undergone multiple surgeries. In addition, there is a tendency for rotation of the intraocular tube into the corneal endothelium as well as reports of external and internal tube erosion. Freedman first described the use of glycerin preserved donor sclera to cover the subconjunctival portion of the glaucoma implant tube in 1987 [15]. Since that time, use of various other materials has been described, including pericardium, amniotic membrane, fascia lata, dura, and corneal tissue. At this time, the majority of glaucoma implant tubes are covered with two graft materials: cornea and pericardium.

Processed pericardial tissue is a well-described patch graft material that has been in use since 1998, when its advantages over donor sclera were first described by Raviv et al. [16]. Its advantages include widespread availability without dependence of an eye bank, 5-year shelf life, uniform size and tissue quality and enhanced sterility. Similar characteristics are also offered by processed scleral tissue.

Glycerol preserved corneal tissue and irradiated corneal tissue have more recently become available for shunt tube coverage. Corneal patch grafts offer improved cosmesis, and enhanced visibility for laser suture lysis, in addition to a similar 5-year shelf life. A 2012 comparison between glycerol preserved corneal tissue and processed pericardium indicated that glycerol preserved cornea may significantly decrease the rate of tube exposure while providing a longer time to initial exposure event [17].

Summary for the Clinician

- Processed pericardium, processed sclera, and processed cornea all offer similar safety profiles, widespread availability, and 5-year shelf lives.
- There is no high quality evidence to support the statement that any one material is better than another.

38.8 Should My Surgical Technique Change if the Eye Is Aphakic?

The aphakic eye presents special concerns, as well as special opportunities. The aphakic eye often has a complex surgical history. It may be at higher risk for retinal detachment or choroidal hemorrhage. It may also be dependent on a contact lens for best vision.

If the patient wears or intends to wear a contact lens for aphakic correction, a tube shunt is definitely preferable to a trabeculectomy as a drainage procedure. If the tube is to be placed in the anterior chamber, preoperative gonioscopy is important to assess the intended insertion site internally. In addition, careful examination for the presence of vitreous in the anterior chamber must be done. If it is found, meticulous anterior vitrectomy must be done as part of the implant surgery.

The aphakic status of an eye opens up the possibility of pars plana tube insertion. This requires a history of complete prior vitrectomy or a full vitrectomy at the time of implantation. A "core vitrectomy" is not adequate, as the anterior peripheral vitreous must be removed. There are several advantages to pars plana insertion. The surgery is done far from the limbus so that prior scarring or atrophy of anterior conjunctiva is not likely to be an issue. Pars plana insertion also avoids potential interaction of the tube with anatomic abnormalities such as peripheral anterior synechias, iris distortions, or lens remnants. In addition, if the cornea is compromised, pars plana insertion may be a safer option. Later implantation of an AC IOL is usually simplified with the tube posteriorly placed. If a pars plana sutured lens is used later, it must be fixated at sites away from the tube insertion.

In summary, tube shunt surgery is often a good choice for managing glaucoma in an

aphakic eye, but special care must be taken to anticipate and prevent vitreous blockade of the tube.

Summary for the Clinician

- Tube shunts are a good option in aphakes who wear a contact lens.
- Aphakia provides an opportunity for pars plana insertion.
- A complete anterior peripheral vitrectomy is needed for pars plana insertion.

38.9 Should Technique Change if the Patient Has a Great Deal of PAS?

Most surgeons introduce the tube into the anterior chamber through a 23-gauge needle tract made in the anterior chamber angle. Usually, the tube will not be in contact with either the iris or the cornea with this approach. The presence of PAS may complicate this important step in two ways.

The angle may be relatively open but PAS can bridge the entry path of the tube. This may lead to bleeding and iris disruption when the needle is passed into the eye for tract creation. If the PAS are not extensive, preoperative gonioscopy may reveal an area free of PAS, which can be used for tube placement.

If PAS are more extensive, there may be no unobstructed path for the tube. Extensive anterior synechias may foreshorten the angle. This can greatly reduce the angle space available for tube placement, thereby increasing the chance that the tube will end up in contact with either the iris or the cornea. Perhaps the most challenging such circumstance is neovascular glaucoma, where there is a high probability of complete angle-closure with anterior PAS tenting the whole plane of the iris forward. Further complicating tube implantation in NVG is the possible presence of fragile new vessels that bleed readily from the implant site and may lead to clots occluding outflow.

To summarize regarding peripheral anterior synechias:

1. If the PAS are only intermittent, preoperative gonioscopy should reveal a PAS-free site for implantation.
2. If the PAS are closing the angle completely (or nearly so) AND there is still sufficient space for the tube in the remaining angle, it may be possible to avoid PAS by entering just anterior to them in the false angle.
3. If the PAS are closing the angle completely, and are located quite anteriorly, but the bulk of the iris remains posterior in its normal position, it may be possible to pass the needle, then the tube, though the PAS with the tip coming out just in front of the iris plane.
4. If the PAS that close the angle completely are located anteriorly, and, due to tension on the iris, the iris is also moved anteriorly, then this can greatly reduce the anterior chamber volume. Here, it may be better to make a peripheral iridectomy and direct the tube into the eye so that it stays behind the iris with the tip resting in the opening of the iridectomy. In pseudophakic eyes, the tube can be passed behind the iris.
5. If the anatomy of the anterior chamber is so distorted that the tube cannot be positioned in either the anterior chamber or the posterior chamber, a pars plana insertion may be used.

Summary for the Clinician

- The extent of PAS and their effect on iris anatomy relative to the cornea will affect placement of the tube in the anterior chamber.
- If there is no space in the anterior chamber, the sulcus and pars plana are alternative locations.

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References

1. Budenz DL, Barton K, Gedde SJ, et al. Five-year treatment outcomes in the Ahmed Baerveldt comparison study. Ophthalmology. 2015;122(2):308–16.
2. Christakis PG, Tsai JC, Kalenak JW, et al. The Ahmed versus Baerveldt study: three-year treatment outcomes. Ophthalmology. 2013;120(11):2232–40.
3. Krupin T, Kaufman P, Mandell AI, et al. Long-term results of valve implants in filtering surgery for eyes with neovascular glaucoma. Am J Ophthalmol. 1983;95:775–82.
4. Molteno AC, Straughan JL, Ancker E. Long tube implants in the management of glaucoma. S Afr Med J. 1976;50:1062–6.
5. Heuer DK, Lloyd MA, Abrams DA, et al. Which is better? One or two? A randomized clinical trial of single-plate versus double-plate Molteno implantation for glaucomas in aphakia and pseudophakia. Ophthalmology. 1992;99:1512–9.
6. Lloyd MA, Baerveldt G, Fellenbaum PS, et al. Intermediate-term results of a randomized clinical trial of the 350 mm^2 versus the 500 mm^2 Baerveldt implant. Ophthalmology. 1994;101:1456–63.
7. Britt MT, LaBree LD, Lloyd MA, et al. Randomized trial of the 350 mm^2 versus the 500 mm^2 Baerveldt implant: longer term results: is bigger better? Ophthalmology. 1999;106:2312–8.
8. Minckler DS, Shammas A, Wilcox M, et al. Experimental studies of aqueous filtration using the Molteno implant. Trans Am Ophthalmol Soc. 1987;85:368–92.
9. Schwartz KS, Lee RK, Gedde SJ. Glaucoma drainage implants: a critical comparison of types. Curr Opin Ophthalmol. 2006;17:181–9.
10. Minckler DS, Francis BA, Hodapp EA, et al. Aqueous shunts in glaucoma. Ophthalmology. 2008;115:1089–98.
11. Wilson MR, Mendis U, Smith SD, Paliwal A. Ahmed glaucoma valve implant versus trabeculectomy in the surgical treatment of glaucoma: a randomized clinical trial. Am J Ophthalmol. 2000;130:267–73.
12. Wilson MR, Mendis U, Paliwal A, Haynatzka V. Long term follow-up of primary glaucoma surgery with Ahmed Glaucoma Valve implant versus trabeculectomy. Am J Ophthalmol. 2003;136:464–70.
13. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the tube versus trabeculectomy study after five years of follow-up. Am J Ophthalmol. 2012;153:789–803.
14. Nouri-Mahdavi K, Caprioli J. Evaluation of the hypertensive phase after insertion of the Ahmed Glaucoma Valve. Am J Ophthalmol. 2003;136:1001–8.
15. Freedman J. Scleral patch grafts with Molteno setons. Ophthalmic Surg. 1987;18(7):532–4.
16. Raviv T, et al. Pericardial patch grafts in glaucoma implant surgery. J Glaucoma. 1998;7(1):27–32.
17. Wigton E, Swanner JC, Joiner W, et al. Outcomes of shunt tube coverage with glycerol preserved cornea versus pericardium. J Glaucoma. 2014;23(4):258–61.
18. Molteno AC, Polkinghorne PJ, Bowbyes JA. The vicryl tie technique for inserting a draining implant in the treatment of secondary glaucoma. Aust N Z J Ophthalmol. 1986;14:343–54.
19. Kooner KS, Goode SM. Removable ligature during Molteno implant procedure. Am J Ophthalmol. 1982;114:102–3.
20. Traverso CE, Tomey KF, al-Kaff A. The long-tube single plate Molteno implant for the treatment of recalcitrant glaucoma. Int Ophthalmol. 1989;13:159–62.

Procedural Treatments: New Surgical Options

39

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Core Messages

- The body of literature for new options in glaucoma surgery continues to slowly grow highlighting not only increased efficacy and wider indication for use but also limitations that may reflect complexities in aqueous humor outflow ripe for discovery.
- One of three levels can be assigned to indicate the strength of evidence in support of a treatment modality. One must be aware of flaws in the evidence supporting new treatments for glaucoma.
- New procedures that are gaining popularity include transtrabecular microbypass aqueous shunting to Schlemm's canal (iStent), viscodilation and suture placement in Schlemm's (canaloplasty), endolaser cyclophotocoagulation, and ab interno trabeculotomy (Trabectome).

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39.1 What New Technologies or Surgical Options Have Emerged for the Treatment of Intraocular Pressure in Glaucoma? Is One of the New Technologies More Promising Than the Others? If So, What Is the Evidence?

Commentary in this section is limited to devices that represent new technologies or improvements over preexisting technologies for intraocular pressure (IOP) control that reached the marketplace during or after 1998. Evidence-based support for various technologies is rated by the author according to the American Academy of Ophthalmology's (AAO) scheme as Level I (strong evidence to support it), Level II (substantial evidence), or Level III (weak body of evidence) and the Oxford system, which is based on available peer reviewed publications [1] (see Table 39.1). Commonly used study designs in clinical vision literature are interventional (including therapy), observational (no intervention), or others (meta-analyses and systematic reviews) [2]. To date, few new technologies for glaucoma can be considered well supported by high-level evidence. For many devices, there may be only one or no randomized clinical trials (RCTs) comparing them with existing therapies (highest level of evidence),

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Table 39.1 Levels of evidence-based medicine literature

AAO grade	Oxford level of evidence	Type of study
I	1a	Systematic review (with homogeneity[a]) of RCTs
	1b	Individual RCT (with narrow confidence interval)
	1c	All or none[b]
II	2a	Systematic review (with homogeneity[a]) of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., <80 % follow-up)
	2c	"Outcomes" research
	3a	Systematic review (with homogeneity[a]) of case-control studies
	3b	Individual case-control studies
III	4	Case-series (and poor quality cohort and case-control studies)
III	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Adapted from http://www.cebm.net/index.aspx?o=1025; last accessed 2/20/08

[a]Homogeneity refers to the systematic review being free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies

[b]Met when all patients developed the endpoint before the treatment became available, but some now survive on it; or when some patients developed the endpoint before the treatment became available, but none now develop it with treatment

or the RCTs available may not have been well done. Concerns with the quality of an RCT may revolve around the presence of an adequate control group, sufficiently long follow-up and compliance with the protocol, study execution in a manner that produces reliable and accurate data, the power of the study to adequately detect differences, and whether the analyses were performed using appropriate statistical methods. To evaluate the quality of a randomized trial, readers are advised to view the CONSORT statement (http://www.consort-statement.org/?o=1011). For observational studies, readers may refer to the recently published STROBE document (http://www.annals.org/cgi/content/full/147/8/573). Guidelines for evaluating interventional case series and other study designs most frequently published in clinical vision journals have been published in *Ophthalmology* [2].

39.1.1 Aqueous Shunts for Glaucoma (Supporting Evidence Level I/1c)

The application of aqueous shunts for glaucoma treatment has been reviewed extensively [1, 3] and their important role in the management of complex glaucomas, especially after failure of medical, laser, and traditional surgical therapies. However more recently, expanding the use of aqueous shunt implantation beyond refractory glaucoma has been supported by the results of the Tube versus Trabeculectomy (TVT) study, which was a prospective, randomized, multicenter clinical trial that compared the safety and efficacy of Baerveldt 350 mm^2 shunt (Abbott Medical Optics) to trabeculectomy with mitomycin C (MMC) in patients with previous ocular surgery [4]. The TVT study reported no statistically significant differences between the two procedures in achieving and sustaining IOPs in the low teens over the 5-year study period with similar rates of vision loss, but trabeculectomy was associated with higher risk of failure and greater need for reoperations compared to Baerveldt shunt implantation [5–10].

Supporting literature has rapidly expanded during the recent decade with a few randomized trials comparing Ahmed shunts (New World Medical) to trabeculectomy with MMC [11, 12], to cyclodestructive therapy [13], and to the Baerveldt shunt [14–19]. In particular, two separate, prospective, randomized, multicenter

clinical trials, aptly named the Ahmed Baerveldt Comparison (ABC) study and Ahmed Versus Baerveldt (AVB) study recently compared the Ahmed shunt to the Baerveldt 350 mm^2 shunt and reported similar 3-year results [12–17]. The Baerveldt implant (with a larger surface area) achieved significantly greater long-term IOP reduction with a lesser need for topical glaucoma therapy, but the Ahmed implant (a "valved" device unlike the "non-valved" Baerveldt) was associated with a significantly lower rate of serious postoperative complications in the ABC study [18] and lesser hypotony-related vision threatening complications in the AVB study [19].

39.1.2 Transcleral Cyclodestruction (Supporting Evidence Level III/4)

Traditionally reserved for end-stage and refractory glaucoma, transscleral cyclodestruction (either contact or noncontact Nd:YAG laser versus 810 nm diode laser) [20] is now gathering description as a first line treatment [21, 22] albeit without support of RCTs to date. Some dose response evidence exists for greater IOP reduction with increasing energy delivered [23, 24]. Previously, less predictable outcomes with some serious complications such as phthisis, hypotony, sympathetic ophthalmia [25], malignant glaucoma [26], and/or necrotizing scleritis [27] have been reported. These serious complications are most frequently seen in eyes that are end-stage with poor vision at the time of cyclodestruction. The descriptions of early utilization of transcleral cyclodestruction use an overall lower energy applied in the treatment of open-angle glaucoma eyes that are less advanced, end-staged, or sick. Additionally, there may be a role of transcleral cyclodestruction in patients unable to undergo anesthesia in an operating room secondary to medical comorbidities.

39.1.3 Cyclodestruction with Diode Endocyclophotocoagulation (Supporting Evidence Level I/1c)

Endoscopic photocoagulation (ECP; Endo Optiks) combines a semiconductor diode with a light source in an endoscopic device that allows for precise delivery of laser energy to the ciliary processes to decrease aqueous production while limiting damage to surrounding structures [28]. Its use was first reported in the US literature in 2001 as a treatment for pediatric glaucoma [29, 30]. Initially, the role of ECP was primarily studied in patients who had failed prior glaucoma surgery. ECP provided additional benefit by decreasing IOP and reducing the need for medications while avoiding episcleral and scarred conjunctiva from prior surgeries [31]. In recent years, the role of ECP has expanded. It has been utilized in conjunction with cataract surgery as an initial therapy for mild-to-moderate glaucoma as it can be performed through the same incision and spares tissue for future drainage surgery if needed [32–34]. ECP also has a role in patients who are aphakic or have narrow angles at high risk of complications following filtration surgery [35]. ECP can be titrated to achieve desired IOP lowering by utilizing the pars plana approach and "ECP-plus" technique (treatment of posterior ciliary processes and pars plana) for recalcitrant glaucomas [36]. More recently ECP has been utilized to change the shape of the ciliary processes causing the anterior portion to shrink posteriorly (cilioplasty) (Fig. 39.1) which can lead to greater opening of narrow angles with plateau iris configuration [36, 37].

39.1.4 EX-PRESS Mini-Shunt (Supporting Evidence Level I/1c)

The ExPRESS Mini-Shunt is a variation on trabeculectomy with the theoretical advantages of a

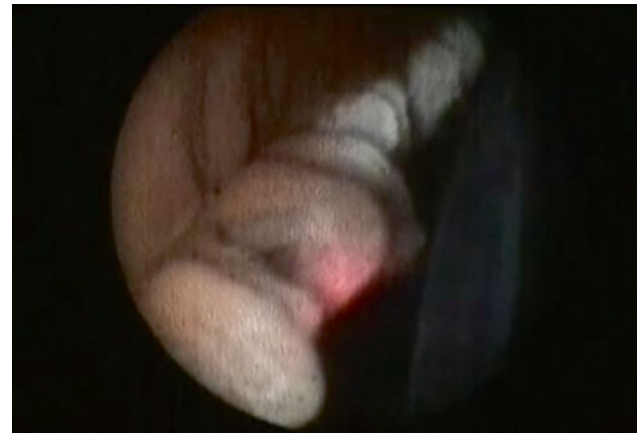

Fig. 39.1 Endoscopic cilioplasty for plateau iris syndrome. Large anteriorly rotated ciliary processes pushing peripheral iris anteriorly are seen in the proximal view and distally (after cilioplasty), where the processes are flattened and shrunken to open the angle more

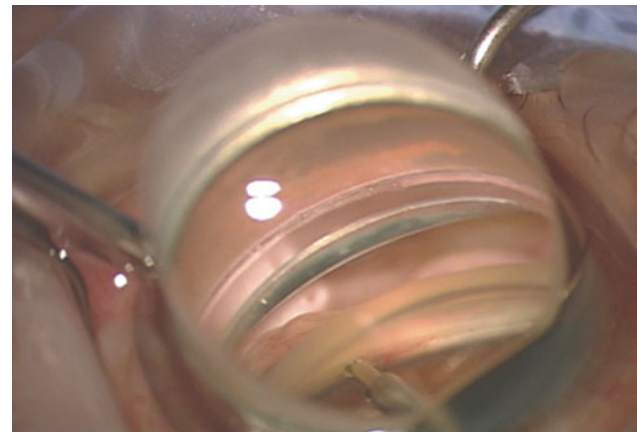

Fig. 39.2 Trabectome creating a cleft in the angle. The view is through a gonioprism intraoperatively

consistently sized scleral fistula and no need for an iridectomy. Multiple RCTs have now been performed with a few meta-analyses [38–40]. Mostly the comparison between trabeculectomy and EX-PRESS demonstrate similar IOP reduction and complications (except there is less postoperative hyphema with EX-PRESS) and earlier vision recovery in the EX-PRESS group. These findings are balanced against the difficulties in conducting and interpreting such studies given the heterogeneous nature and nonuniform trabeculectomy methods in use. Additionally, EX-PRESS is clearly associated with increased costs and possibly decreased cost-effectiveness [41]. As such, compared to trabeculectomy, the EX-PRESS Mini-Shunt while a more standardized procedure may yield small benefits for increased cost ultimately reducing the calculus for its implementation in a cost-benefit analysis.

39.1.5 Ab Interno Trabeculectomy, Trabectome (Supporting Evidence Level II/3b)

The Trabectome (NeoMedix), first utilized in Mexico in 2005 and described in a case series [42, 43], utilizes an electric spark to ablate the trabecular meshwork and inner wall of Schlemm's canal via gonioscopic surgery (Fig. 39.2). The Trabectome handpiece, approved for single-use only, includes an infusion sleeve and an aspiration function. Currently, the use of Trabectome has expanded worldwide and has been used as an alternative to laser trabeculoplasty or filtering surgery in eyes with open-angle glaucoma not responding to medical therapy. It has been used as a first line therapy with or without combined cataract surgery. In adults with POAG, Trabectome has demonstrated a 31 % reduction

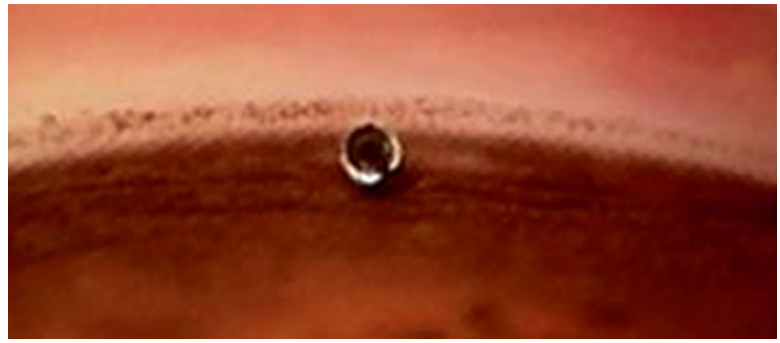

Fig 39.3 Internal view of the Glaukos iStent SUPRA (Courtesy of Glaukos Corporation)

in IOP and 28 % reduction in postoperative medications 1 year after surgery [44]. Complications with the procedure are rare with hyphema being the most common complication [45]. When Trabectome is unsuccessful, it does not reduce efficacy of subsequent filtering procedures [46]. A study that compared outcomes of Trabectome to trabeculectomy demonstrated that while trabeculectomy allowed for greater reduction in IOP at 2 years, 61.3 % vs. 43.5 %, major complications such as hypotony and wound leak were not noted in the Trabectome group [47]. The main advantage of the procedure therefore lies in its ability to lower IOP with an excellent safety profile, which can be utilized in the treatment of mild-to-moderate glaucoma and in those for whom filtering surgery carries greater risk. Additionally, this technology offers advantages for angle surgery in children compared to traditional goniotomy or ab externo trabeculotomy, as it both removes a strip of trabecular meshwork and aspirates tissue debris, which could then block drainage or cause scarring [48]. The long-term efficacy (beyond 1–2 years) of Trabectome is still to be reported and published.

39.1.6 Suprachoroidal Devices (Supporting Evidence Level III/5)

Clinical trials are underway investigating multiple different suprachoroidal shunts, each designed to establish a permanent channel between the anterior chamber and the suprachoroidal space, thereby theoretically avoiding the episcleral fibrosis typically associated with subconjunctival filtration bleb failure. The CyPass Micro-Stent (Transcend-Medical) is a biocompatible polyamide stent (300 μm lumen; 6.35 mm length with 76 μm fenestrations along its distal end) placed ab interno via a clear corneal incision. The iStent SUPRA (Fig. 39.3) (Glaukos; 4 mm length, 165 μm lumen) is made from a heparin coated combination of medical-grade titanium and polyestersulfone and placed ab interno via a clear corneal incision. Published results for CyPass Micro-Stent and iStent Supra are pending in Europe and the United States. The SOLX Gold Shunt (SOLX) is also designed to shunt fluid from the anterior chamber to the suprachoroidal space but differs in its approach from the Cypass Micro-Stent and iStent SUPRA because the Gold Shunt is inserted using an ab externo approach. The anterior end of this biocompatible, 24-karat gold SOLX device (5.2 mm long, 3.2 mm wide, and 44–68 μm thickness) is placed into the anterior chamber over the scleral spur. Additional channels may be opened in the device postoperatively to further lower IOP using a laser focused through the clear cornea. Flow-resistance is stated to be 0.65–1.3 mmHg/μL/min. Published evidence is limited, since results are pending from two major European studies (CyCLE and DUETTE), as well as from the COMPASS clinical study in the United States investigating the Gold Shunt [49, 50].

In the past, suprachoroidal shunts were not successful, including a variety of nonlumened setons constructed of various materials. The past

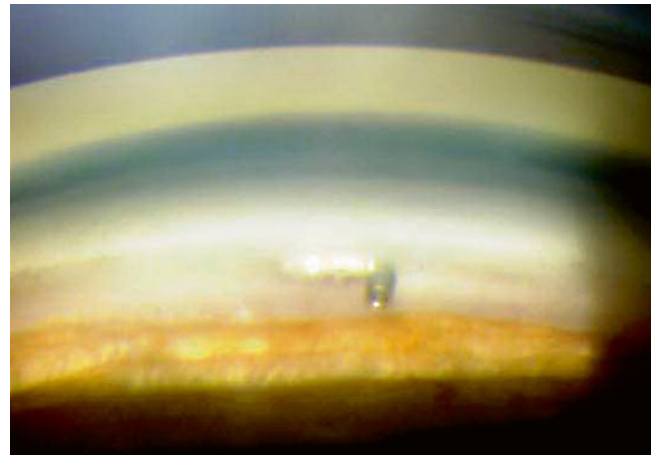

Fig. 39.4 Gonioscopic view of the iStent shunt properly located in Schlemm's canal

failures were most likely due to fibrous tissue relatively impenetrable to aqueous outflow walling off the posterior portion of the devices. Data both short term and long term on these new suprachoroidal devices, using new materials and designs, are awaited.

39.1.7 Trans-Trabecular Micro Bypass Shunt (Supporting Evidence Level II/2a)

The iStent (Glaukos, Inc.) is an FDA-approved device for mild-to-moderate glaucoma treatment concurrent with cataract surgery. The mechanism of action is through trabecular meshwork bypass (Fig. 39.4) that complements the ablation methods described above. Theoretical advantages include the enhancement of native outflow pathways with preservation of conjunctiva (thereby maintaining options for future trabeculectomies and aqueous shunts) in a disposable delivery system. One RCT comparing phacoemulsification alone to phacoemulsification combined with one iStent placement has shown reduction in IOP and glaucoma medication burden, although the effects may have diminished with time [51, 52]. Uncontrolled studies suggest greater IOP reduction with an increased number of iStents placed [53]. Second generation stents (GTS-400) simplify stent placement. A handful of prospective studies (with one RCT) demonstrate IOP reduction equivalent to medical management with placement of multiple second generation stents as a stand-alone procedure without concurrent cataract surgery [54–56].

39.1.8 Canaloplasty (II/2b)

Canaloplasty (Fig. 39.5), now distributed by Ellex, is a glaucoma surgery whose steps involve (a) creation of two scleral flaps with a deep sclerectomy, (b) leading to the formation of a trabeculo-descemet window (TDW) that acts as a non-penetrating filter to aqueous humor percolation out of the eye, (c) followed by an unroofing of Schlemm's canal (SC), (d) leading to passing of a lighted fiberoptic probe 360° through SC, (e) followed by reversal of the fiberoptic probe back out of the eye with a prolene stent and concurrent release of viscoelastic into SC 360°, (f) and ending with tying of the prolene suture to distend the canal inward, (g) with closure of the primary scleral flap and conjunctival wounds [57]. As such, there may be multiple mechanisms of IOP reduction with canaloplasty as this surgery can work as a variation of the commonly performed European deep sclerectomy [58] with a possible bleb (steps A/B), a viscocanulostomy [59] which possibly involves trabecular meshwork breaks (steps C/E), a stenting of SC to prevent SC collapse (steps D/F), a trabeculectomy variation (if the TDW is inadvertently broken), or all of the above. Multiple prospective non-RCTs have been performed with 3–4 year follow-up showing encouraging IOP reduction to the mid-to-high teens with a low

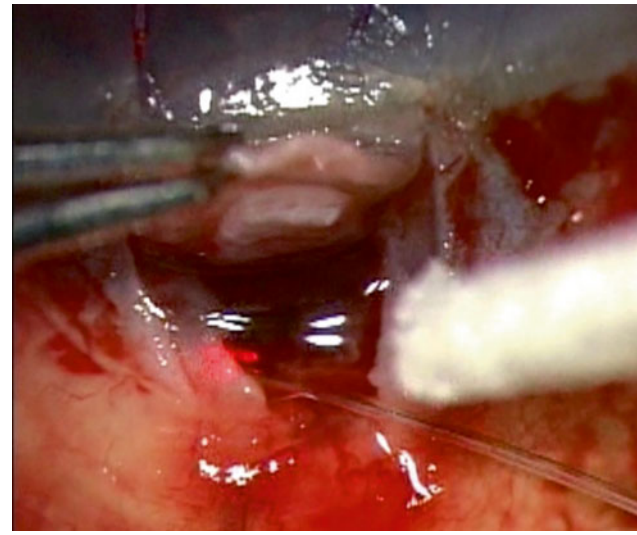

Fig 39.5 Canaloplasty demonstrating the flaps from the superficial and deep sclerectomy with the fiberoptic probe being passed through Schlemm's canal

complication rate and decrease of glaucoma medicine burden [60–63]. Disadvantages of canaloplasty include conjunctival involvement of surgery with a higher learning curve.

Summary for the Clinician

- Several new technologies discussed in this chapter hold promise as treatments for IOP in glaucoma, particularly in mild-to-moderate glaucoma or in combination with cataract surgery.
- The traditional assumption has been that episcleral venous pressure (±8 mmHg) accounts for the lower limit of IOP achievable by eliminating the resistance of the meshwork-juxtacanalicular complex. Since IOP outcomes with trabecular bypass or shunting are usually higher, it is obvious that we do not fully understand the physiology of the outflow channels and aqueous veins.
- Surely, future studies, hopefully including greater and better randomized trials or other comparative studies, will clarify the specific indications for all of these devices.

References

1. Minckler DS, Francis BA, Hodapp EA, et al. Aqueous shunts in glaucoma: a report by the American Academy of Ophthalmology. Ophthalmology. 2008;115:1089–98.
2. Minckler D. Study design scheme, structured abstract sections and study design worksheets, [appendix to instructions for authors; page 185]. Ophthalmology. 1999;106:185–206.
3. Minckler DS, Vedula SS, Li TJ, et al. Aqueous shunts for glaucoma (Cochrane review). Cochrane Database Syst Rev. 2006;2, CD004918.
4. Gedde SJ, Schiffman JC, Feuer WJ, et al. The Tube Versus Trabeculectomy study: design and baseline characteristics of study patients. Am J Ophthalmol. 2005;140:275–87.
5. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy Study after one year of follow-up. Am J Ophthalmol. 2007;143:9–22.
6. Gedde SJ, Schiffman JC, Feuer WJ, et al. Three-year follow-up of the Tube Versus Trabeculectomy Study. Am J Ophthalmol. 2009;148:670–84.
7. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) Study after five years of follow-up. Am J Ophthalmol. 2012;153:789–803.
8. Gedde SJ, Herndon LW, Brandt JD, et al. Surgical complications in the Tube Versus Trabeculectomy Study during the first year of follow-up. Am J Ophthalmol. 2007;143:23–31.
9. Gedde SJ, Herndon LW, Brandt JD, et al. Postoperative complications in the Tube Versus Trabeculectomy (TVT) Study during five years of follow-up. Am J Ophthalmol. 2012;153:804–14.

10. Rauscher FM, Gedde SJ, Schiffman JC, et al. Motility disturbances in the Tube Versus Trabeculectomy Study during the first year of follow-up. Am J Ophthalmol. 2009;147:458–66.
11. Wilson MR, Mendis U, Smith SD, et al. Ahmed glaucoma valve implant vs. trabeculectomy in the surgical treatment of glaucoma: a randomized clinical trial. Am J Ophthalmol. 2000;130:267–73.
12. Wilson MR, Mendis U, Paliwal A, et al. Long-term follow-up of primary glaucoma surgery with Ahmed glaucoma valve implant versus trabeculectomy. Am J Ophthalmol. 2003;136:464–70.
13. Lima FE, Magacho L, Carvalho DM, et al. A prospective, comparative study between endoscopic cyclophotocoagulation and the Ahmed drainage implant in refractory glaucoma. J Glaucoma. 2004;13:233–7.
14. Barton K, Gedde SJ, Budenz DL, et al. The Ahmed Baerveldt Comparison Study: methodology, baseline patient characteristics, and intraoperative complications. Ophthalmology. 2011;118:435–42.
15. Christakis PG, Kalenak JW, Zurakowski D, et al. The Ahmed Versus Baerveldt Study. Design, baseline characteristics, and intraoperative complications. Ophthalmology. 2011;118:2172–9.
16. Budenz DL, Barton K, Feuer WJ, et al. Treatment outcomes in the Ahmed Baerveldt Comparison Study after one year of follow-up. Ophthalmology. 2011;118:443–52.
17. Christakis PG, Tsai JC, Zurakowski D, et al. The Ahmed Versus Baerveldt Study. One-year treatment outcomes. Ophthalmology. 2011;118:2180–9.
18. Barton K, Feuer WJ, Budenz DL, et al. Three-year outcomes in the Ahmed Baerveldt Comparison (ABC) Study. Ophthalmology. 2014;121(8):1547–57.
19. Christakis PG, Tsai JC, Kalenak JW, et al. The Ahmed Versus Baerveldt Study. Three-year treatment outcomes. Ophthalmology. 2013;120:2232–40.
20. Huang G, Lin SC. When should we give up filtration surgery: indications, techniques and results of cyclodestruction. Dev Ophthalmol. 2012;50:173–83.
21. Lai JS, Tham CC, Chan JC, Lam DS. Diode laser transscleral cyclophotocoagulation as primary surgical treatment for medically uncontrolled chronic angle closure glaucoma: long-term clinical outcomes. J Glaucoma. 2005;14:114–9.
22. Grueb M, Rohrbach JM, Bartz-Schmidt KU, Schlote T. Transscleral diode laser cyclophotocoagulation as primary and secondary surgical treatment in primary open-angle and pseudoexfoliatve glaucoma. Long-term clinical outcomes. Graefes Arch Clin Exp Ophthalmol. 2006;244:1293–9.
23. Murphy CC, Burnett CA, Spry PG, Broadway DC, Diamond JP. A two centre study of the dose-response relation for transscleral diode laser cyclophotocoagulation in refractory glaucoma. Br J Ophthalmol. 2003;87:1252–7.
24. Hauber FA, Scherer WJ. Influence of total energy delivery on success rate after contact diode laser transscleral cyclophotocoagulation: a retrospective case review and meta-analysis. J Glaucoma. 2002;11:329–33.
25. Albahlal A, Al Dhibi H, Al Shahwan S, Khandekar R, Edward DP. Sympathetic ophthalmia following diode laser cyclophotocoagulation. Br J Ophthalmol. 2014;98:1101–6.
26. Muqit MM, Menage MJ. Malignant glaucoma after phacoemulsification: treatment with diode laser cyclophotocoagulation. J Cataract Refract Surg. 2007;33:130–2.
27. Shen SY, Lai JS, Lam DS. Necrotizing scleritis following diode laser transscleral cyclophotocoagulation. Ophthalmic Surg Lasers Imaging. 2004;35:251–3.
28. Uram M. Endoscopic cyclophotocoagulation in glaucoma management. Curr Opin Ophthalmol. 1995;6: 19–29.
29. Neely DE, Plager DA. Endocyclophotocoagulation for management of difficult pediatric glaucomas. J AAPOS. 2001;5:221–9.
30. Lin SC. Endoscopic and Transcleral cyclophotocoagulation for the treatment of refractory glaucoma. J Glaucoma. 2008;17:238–47.
31. Francis BA, Kawji AS, Vo NT, Dustin L, Chopra V. Endoscopic cyclophotocoagulation (ECP) in management of uncontrolled glaucoma with prior aqueous tube shunt. J Glaucoma. 2011;20:523–7.
32. Uram M. Combined phacoemulsification, endoscopic ciliary process photocoagulation, and intraocular lens implantation in glaucoma management. Ophthalmic Surg. 1995;26:346–52.
33. Gayton JL, Van Der Karr M, Sanders V. Combined cataract and glaucoma surgery: trabeculectomy versus endoscopic laser cycloablation. J Cataract Refract Surg. 1995;25:1214–9.
34. Francis BA, Berke SJ, Dustin L, Noecker R. Endoscopic cyclophotocoagulation combined with phacoemulsification alone in medically controlled glaucoma. J Cataract Refract Surg. 2014;40:1313–21.
35. Chen J, Cohn RA, Lin SC, et al. Endoscopic photocoagulation of the ciliary body for the treatment of refractory glaucomas. Am J Ophthalmol. 1999;124: 787–96.
36. Francis BA, Kwon J, Felman R, et al. Endoscopic ophthalmic surgery of the anterior segment. Surv Ophthalmol. 2014;59:217–31.
37. Ahmed IK, Podbielski DW, Naqi A, et al. Endoscopic cycloplasty in angle closure glaucoma secondary to plateau iris. Poster presentation at: AGS annual meeting; 2009, Mar 5–8; San Diego.
38. Chen G, Li W, Jiang F, Mao S, Tong Y. Ex-PRESS implantation versus trabeculectomy in open-angle glaucoma: a meta-analysis of randomized controlled clinical trials. PLoS One. 2014;9:e86045.
39. Wang W, Zhang X. Meta-analysis of randomized controlled trials comparing EX-PRESS implantation with trabeculectomy for open-angle glaucoma. PLoS One. 2014;9(6):e100578.

40. Wang W, Zhou M, Huang W, Zhang X. Ex-PRESS implantation versus trabeculectomy in uncontrolled glaucoma: a meta-analysis. PLoS One. 2013;8(5): e63591.
41. Patel HY, Wagschal LD, Trope GE, Buys YM. Economic analysis of the Ex-PRESS miniature glaucoma device versus trabeculectomy. J Glaucoma. 2014;23:385–90.
42. Minckler DS, Baerveldt G, Alfaro MR, et al. Clinical results with the Trabectome for treatment of open-angle glaucoma. Ophthalmology. 2005;112:962–7.
43. Minckler DS, Baerveldt G, Ramirez MA, et al. Clinical results with the Trabectome, a novel surgical device for treatment of adult open-angle glaucoma. Trans Am Ophthalmol Soc. 2006;104:40–50.
44. Mosaed S, Rhee DJ, Filippopoulos T, et al. Trabectome outcomes in adult open angle glaucoma patients: one year follow-up. Clin Surg Ophthalmol. 2010;28:8.
45. Minckler DS, Mosaed S, Dustin L, et al. Trabectome (Trabeculectomy- internal approach): additional experience and extended follow-up. Trans Am Ophthalmol Soc. 2008;106:1–12.
46. Jea SY, Mosaed S, Vold SD, et al. Effect of a failed trabectome on subsequent trabeculectomy. J Glaucoma. 2012;2:71–5.
47. Jea SY, Francis BA, Vakili G, et al. Ab interno trabeculectomy versus trabeculectomy for open-angle glaucoma. Ophthalmology. 2012;119:36–42.
48. Morales J, Al Shahwan S, Al Odhayb S, et al. Current surgical options for the management of pediatric glaucoma. J Ophthalmol. 2013;2013, 763735.
49. Melamed S, Ben Simon GJ, Goldenfeld M, et al. Efficacy and safety of gold micro shunt implantation to the supraciliary space in patients with glaucoma: a pilot study. Arch Ophthalmol. 2009;127:264–9.
50. Rękas M, Pawlik B, Grala B, et al. Clinical and morphological evaluation of gold micro shunt after unsuccessful surgical treatment of patients with primary open-angle glaucoma. Eye (Lond). 2013;27:1214–7.
51. Craven ER, Katz LJ, Wells JM, Giamporcaro JE. Cataract surgery with trabecular micro-bypass stent implantation in patients with mild-to-moderate open-angle glaucoma and cataract: two-year follow-up. J Cataract Refract Surg. 2012;38:1339–45.
52. Samuelson TW, Katz LJ, Wells JM, Duh YJ, Giamporcaro JE. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. Ophthalmology. 2011;118:459–67.
53. Belovay GW, Naqi A, Chan BJ, Rateb M, Ahmed II. Using multiple trabecular micro-bypass stents in cataract patients to treat open-angle glaucoma. J Cataract Refract Surg. 2012;38:1911–7.
54. Fea AM, Belda JI, Rekas M, et al. Prospective unmasked randomized evaluation of the iStent inject ((R)) versus two ocular hypotensive agents in patients with primary open-angle glaucoma. Clin Ophthalmol. 2014;8:875–82.
55. Ahmed II, Katz LJ, Chang DF, et al. Prospective evaluation of microinvasive glaucoma surgery with trabecular microbypass stents and prostaglandin in open-angle glaucoma. J Cataract Refract Surg. 2014;40:1295–300.
56. Voskanyan L, Garcia-Feijoo J, Belda JI, Fea A, Junemann A, Baudouin C. Prospective, unmasked evaluation of the iStent(R) inject system for open-angle glaucoma: synergy trial. Adv Ther. 2014;31:189–201.
57. Lewis RA, von Wolff K, Tetz M, et al. Canaloplasty: circumferential viscodilation and tensioning of Schlemm's canal using a flexible microcatheter for the treatment of open-angle glaucoma in adults: interim clinical study analysis. J Cataract Refract Surg. 2007;33:1217–26.
58. Roy S, Mermoud A. Deep sclerectomy. Dev Ophthalmol. 2012;50:29–36.
59. Stegmann R, Pienaar A, Miller D. Viscocanalostomy for open-angle glaucoma in black African patients. J Cataract Refract Surg. 1999;25:316–22.
60. Brusini P. Canaloplasty in open-angle glaucoma surgery: a four-year follow-up. ScientificWorldJournal. 2014;2014:1–7. Article ID 469609.
61. Grieshaber MC, Pienaar A, Olivier J, Stegmann R. Canaloplasty for primary open-angle glaucoma: long-term outcome. Br J Ophthalmol. 2010;94: 1478–82.
62. Lewis RA, von Wolff K, Tetz M, et al. Canaloplasty: three-year results of circumferential viscodilation and tensioning of Schlemm canal using a microcatheter to treat open-angle glaucoma. J Cataract Refract Surg. 2011;37:682–90.
63. Bull H, von Wolff K, Korber N, Tetz M. Three-year canaloplasty outcomes for the treatment of open-angle glaucoma: European study results. Graefes Arch Clin Exp Ophthalmol. 2011;249:1537–45.

Procedural Treatments: EX-PRESS Mini Glaucoma Shunt

40

Marlene R. Moster and Wanda D. Hu

Core Messages

- The EX-PRESS glaucoma shunt can be used as a pressure lowering device in patients who have failed prior glaucoma surgery, or as a primary procedure.
- The EX-PRESS has been widely adopted but has not replaced trabeculectomy.
- The procedure for implantation is similar to standard Mitomycin-C trabeculectomy surgery.
- The EX-PRESS shunt offers unique advantages and disadvantages over trabeculectomy, especially in terms of complications.

40.1 How Often Is the EX-PRESS Mini-Shunt Being Used in Place of More Traditional Glaucoma Surgery? Have Glaucoma Specialists Adopted This Surgery?

The EX-PRESS® glaucoma filtration device (Alcon Laboratories, Fort Worth, Texas, USA) is a miniature stainless steel glaucoma implant approved by the FDA in March 2002 that has been in use since then all over the world for the treatment of glaucoma. Over the past 5 years in the United States, about 15,000 implantations have been performed each year in hospitals and ambulatory surgery centers to treat primary, secondary, pseudophakic, and refractory glaucomas. Advocates of its use cite more reliable outcomes, which are attributed to the uniformly sized outflow path for aqueous flow. Those who have not adopted it cite the increased cost incurred by using the device and the small number of prospective randomized controlled trials to show any superiority over trabeculectomy [1].

Summary for the Clinician

- Many eye surgeons and glaucoma specialists have utilized the EX-PRESS mini-shunt in their surgical practice for different types of glaucoma.

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- Those who have not adopted it cite the increased cost to the medical system incurred by its utilization despite similar long-term IOP control in multiple retrospective and prospective studies.

40.2 What Is the EX-PRESS Mini-Shunt and How Does It Work?

The EX-PRESS glaucoma implant is a 400 μm stainless steel (Fig. 40.1) MRI compatible and biocompatible device [2]. It was designed with the intention of offering an accurate, repeatable, and safer alternative to the primary surgical standard of care, which for decades has been the trabeculectomy. Similar to trabeculectomy, the shunt reduces intraocular pressure (IOP) by diverting aqueous humor from the anterior chamber to the subconjunctival space in order to form a filtration bleb [3]. Mitomycin-C (MMC) use during the procedure is recommended to prevent scarring. The device's unique flow-modulating design and the scleral flap under which it is implanted, control postoperative aqueous flow. Filtering surgery with the EX-PRESS mini-shunt is a safe and standardized procedure and as effective as trabeculectomy [4].

Originally the EX-PRESS manufacturer recommended placing the device directly under the conjunctiva, but due to excessive hypotony, exposure, and other adverse effects, this technique has been abandoned [5, 6]. Dahan and Carmichael first recommended implanting the EX-PRESS shunt under a 5×5 mm partial thickness scleral flap, similar to a standard limbus-based guarded trabeculectomy [7]. Placing the EX-PRESS under a half thickness scleral flap provides resistance to aqueous flow and prevents erosion. No iridectomy is required. In their initial case series of 24 eyes, MMC was placed *under* the scleral flap in all cases. They noted a 46 % decrease in IOP and a significant reduction in the need for medications at 1 year. However there was still a 20.8 % hypotony rate with two patients (8.3 %) developing choroidal effusions—one of which required drainage. In an effort to decrease the incidence of hypotony further, we recommend

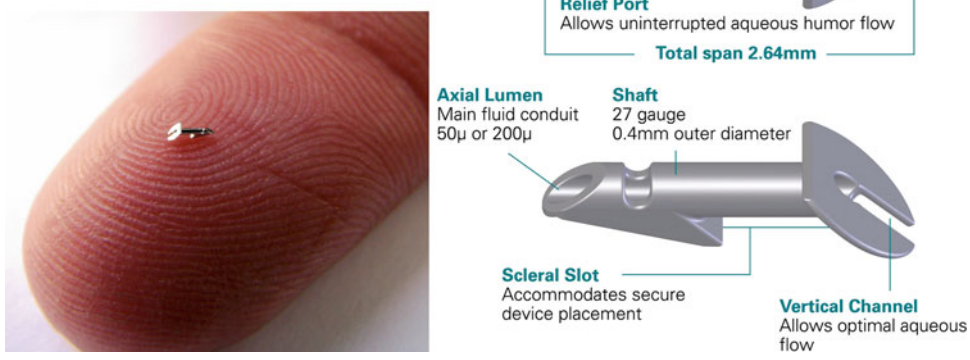

Fig. 40.1 EX-PRESS features. Despite its miniature size, the EX-PRESS features several major structural elements. *Axial orifice*: a conduit for draining aqueous humor from the anterior chamber to the intrascleral space. *External plate*: prevents excessive penetration. *A spur*: prevents extrusion of the EX-PRESS™ from the eye. *Transverse orifices*: near the distal end, which constitute an alternative conduit for aqueous humor drainage in case of occlusion of the primary (axial) opening of the shunt by the iris

placing the MMC on the sclera (0.4 mg/cm^3 for 1.5 min) prior to fashioning the scleral flap to avoid toxicity from MMC.

Summary for the Clinician

- The EX-PRESS glaucoma shunt is a stainless steel device with a flow-modulating design.
- This device is MRI compatible.
- The device does not cause inflammation as the stainless steel is biocompatible.
- The EX-PRESS shunt can be used as an alternative to trabeculectomy in patients who have had prior ocular surgery or as a primary procedure.

40.3 What Are the EX-PRESS Mini-Shunt's Dimensions? How Is It Implanted?

There are currently two models of the EX-PRESS mini-shunt. Detailed information can be seen in Table 40.1. The EX-PRESS shunt's length is only 2.64 mm in length with an internal lumen diameter choice of either 50 or 200 μm. The EX-PRESS glaucoma implant allows for restricted aqueous humor flow from the anterior chamber to the subconjunctival space, thereby reducing the IOP. More commonly, the model with the 50 μm lumen is used for filtering surgery and it is introduced through the limbus with a disposable preloaded inserter (Fig. 40.2) [8]. A 27-gauge needle for the R50 model, or a 25-gauge needle for the P50, is needed to create the anterior chamber entrance for the device. A scleral flap of one-third to one-half scleral thickness is necessary for the success of the procedure, as it will protect the device from erosion through the conjunctiva and help restrict aqueous flow in the early post-op period. Typically, MMC 0.4 mg/cm^3 (although other concentrations can be used per the surgeon's preference), is applied under the conjunctiva and tenons capsule for 1.5 min before the scleral flap is outlined (Fig. 40.3). Scleral flap size is usually 4 mm in both width and height (Fig. 40.4). The entry point into the anterior chamber is at the gray line where the junction of the cornea and sclera meet (Fig. 40.5). Entry into the anterior chamber is made when the chamber is inflated to an IOP of about 20 mmHg through a previously placed paracentesis. The needle entry is directed parallel to the iris and posterior to the cornea so that the corneal stroma is not involved in the insertion. Perfect positioning of the device is obtained when the shunt is in the mid-anterior chamber and flush with the sclera (Fig. 40.6). In its final position, the device should not produce corneal striae or be buried within iris stroma. When the EX-PRESS is properly positioned, immediate flow is noted through the 50 μm lumen. Aqueous flow is directed posteriorly and can be further modified by adjusting either the permanent or releasable sutures at the scleral flap (Fig. 40.7). The goal is to ensure immediate aqueous flow, thereby forming a low, diffuse posterior filtering bleb with microcyst formation within the first 1–2 days. When using a fornix-based flap (suture closure at the limbus), extreme care is advised to assure a water-tight wound. If there is leakage at the limbus (positive Seidel test), it is unlikely

Table 40.1 Current EX-PRESS model features and dimensions

	EX-PRESS®	EX-PRESS®
	P-50	P-200
		
	Beveled tip for easy insertion. Vertical split back plate for posterior flow	
External body shape	Round	
Device length (mm)	2.64	
Internal lumen size (μm)	50	200
Tip shape	Pointed	
Back plate shape	Vertical split	
Preincision needle gauge	25 G	

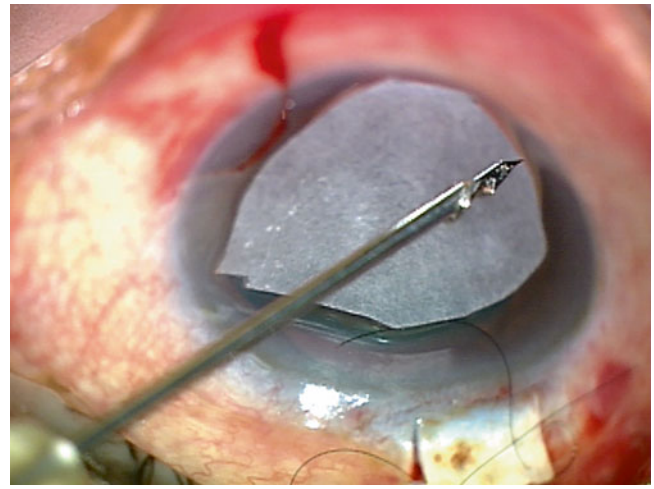

Fig. 40.2 The EX-PRESS shunt on the preloaded inserter

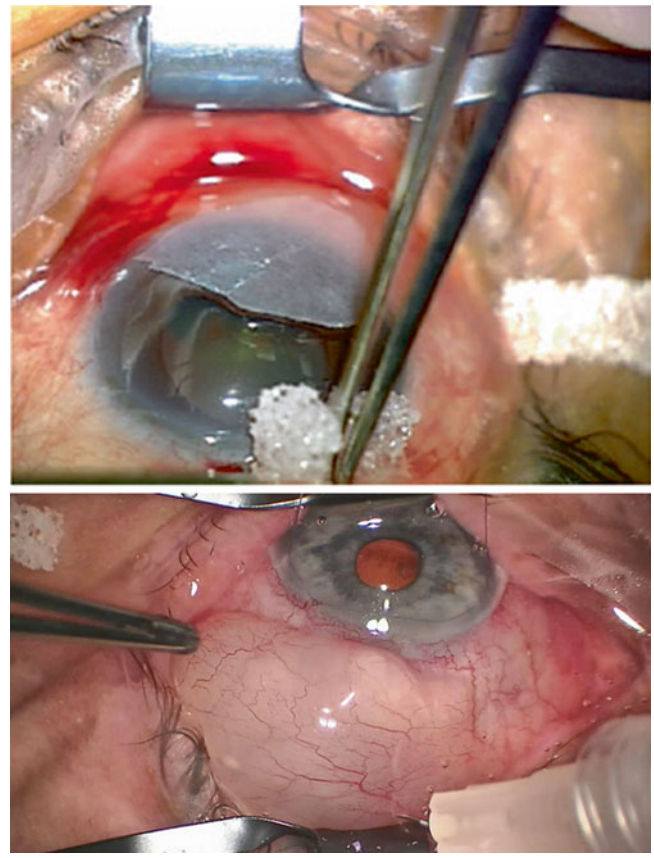

Fig. 40.3 Mitomycin-C (0.4 mg/cm^3) is placed on four cut strips fashioned from a wick (Beaver Visitec International, Waltham, MA). This is left under the conjunctiva and tenon's capsule for 1.5 min before being irrigated copiously with balanced salt solution. The drain is then changed and disposed of properly. Alternatively, a mixture of 1:1 mitomycin-C (0.4 mmg/cm^3) totaling 0.1 cm^3 and Lidocaine 1 % nonpreserved totaling 0.1 cm^3 can be injected under the conjunctiva and tenon's capsule on a 30-gauge needle. Total volume 0.2 cm^3. This does not have to be irrigated out

that a posterior bleb will form and the procedure will likely fail (Fig. 40.8). A bandage contact lens or additional sutures are recommended to rectify this situation. Similar to a trabeculectomy, a combination of steroids, antibiotics, and occasionally nonsteroidal drugs are used postoperatively. The antibiotics are stopped at 1 week, and the steroids are tapered over 4–6 weeks. This procedure can be done easily with a combination of topical and subconjunctival anesthesia known as the blitz anesthesia technique [9]. Typically, 2 % lidocaine jelly (AstraZeneca

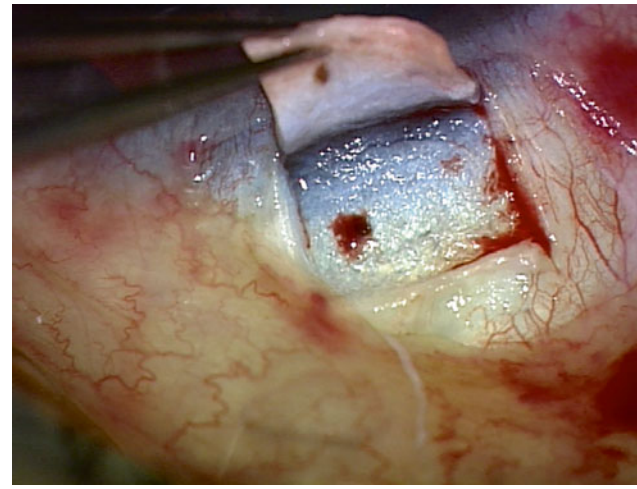

Fig. 40.4 The scleral flap is usually 1/2 to 1/3 scleral thickness and 4×4 mm in dimension

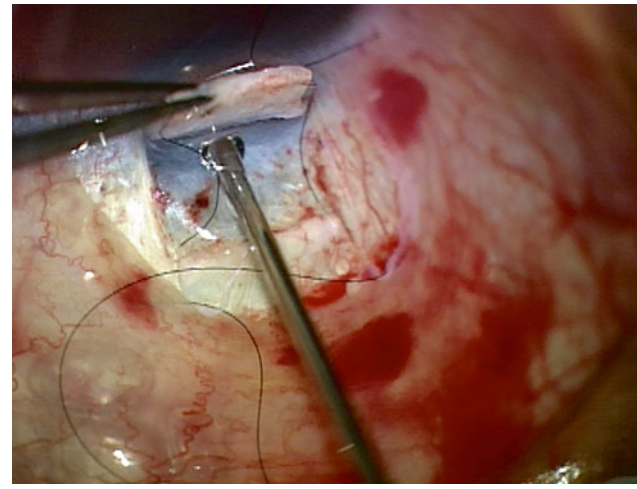

Fig. 40.5 The shunt is inserted through a previously made opening with either a 27- or 25-gauge needle (depending on model used) at the gray line. When the EX-PRESS enters the anterior chamber there is a slight tactile "pop" when the shunt's spur clears the cornea and is solidly within the anterior chamber. Firm pressure on the inserter causes immediate release of the device

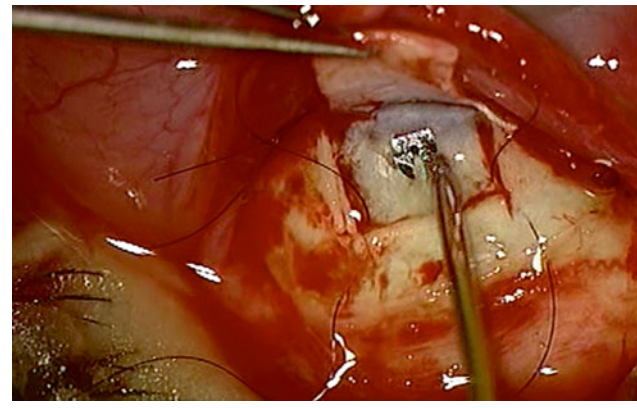

Fig. 40.6 The EX-PRESS external plate should lie flush with the sclera. There is immediate egress of aqueous noted through the 50 μm conduit

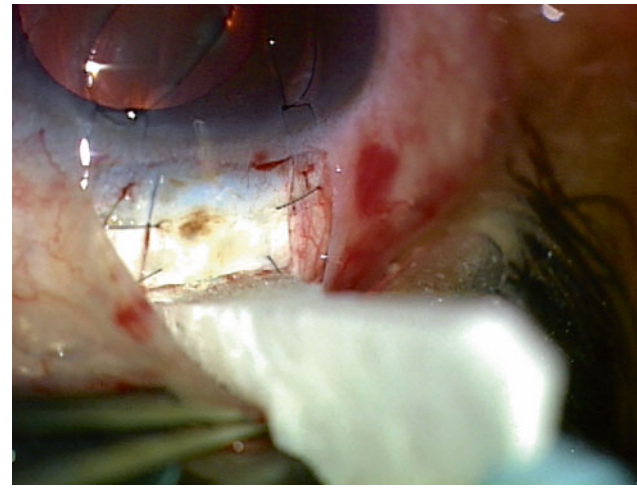

Fig. 40.7 The flow of aqueous should be directed posteriorly and can be modified with placement of sutures. Releasable or laserable sutures work equally well

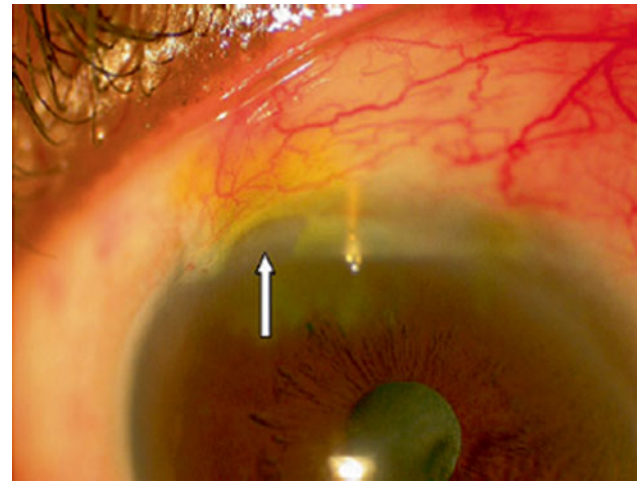

Fig. 40.8 Poor healing of the conjunctiva and a Seidel positive wound leak will lead to failure of the procedure if not corrected. Note the vascularized bleb

PLC) is placed on the eye in the pre-op area 5 min prior to surgery. When in the operating room, 0.1 mL of 1 % lidocaine nonpreserved solution is injected with a cannula intracamerally through a paracentesis (Fig. 40.9). When the conjunctiva is lifted to form a fornix-based flap, additional lidocaine solution is injected with the cannula in the sub-tenon's space. Prior to inserting the EX-PRESS shunt, irrigation with nonpreserved lidocaine 1 % is repeated at the surgical site and it is recommended again before closure of the fornix-based flap.

Summary for the Clinician

- The EX-PRESS allows for the establishment of a low, diffuse posterior bleb if placed correctly in the anterior chamber.
- A scleral flap should be made as one would do for a trabeculectomy after treatment with mitomycin-C.
- Entry into the anterior chamber occurs underneath the scleral flap with a

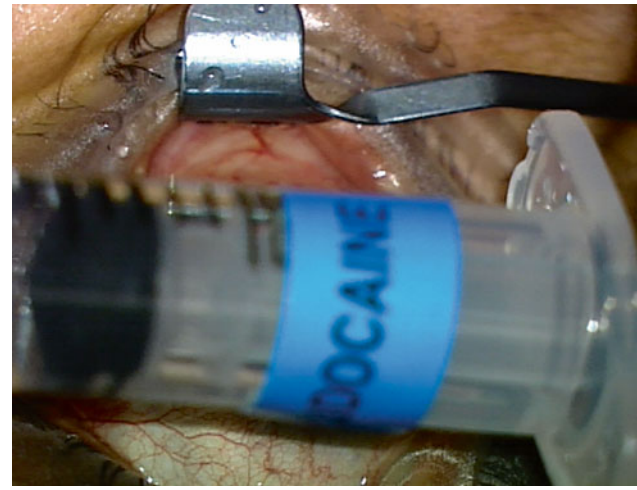

Fig. 40.9 Lidocaine 1 % nonpreserved (0.1 cm^3) is injected through a paracentesis on a cannula at the beginning of the case. Additional lidocaine is placed under the fornix-based conjunctival flap and again prior to inserting the EX-PRESS and closing the conjunctiva

25-gauge needle at the gray line, parallel to the iris, avoiding the corneal stroma.

- The inserter, preloaded with the EX-PRESS shunt, is introduced so that the shunt resides in the mid-anterior chamber. Firm pressure on the inserter causes immediate release of the shunt.
- A water-tight conjunctival closure is necessary to assure success with this device.

40.4 Should An EX-PRESS Mini-Shunt Procedure Be Performed in Place of a Trabeculectomy?

The EX-PRESS shunt demonstrates various advantages over other filtering procedures because it can be implanted at the limbus in spite of minimal remaining healthy conjunctiva (Fig. 40.10). The device is easily placed either temporally or nasally in an eye with prior scarring, as long as there are 2–3 clock hours of mobile superior conjunctiva available (Fig. 40.11). Since the resulting blebs are usually low and diffuse, there is little risk of developing dellen or bleb dysesthesia, even when the surgery is located off to one side. In eyes with prior failed trabeculectomies, the EX-PRESS shunt can reestablish aqueous flow without having to repeat the original failed procedure (Fig. 40.12). The EX-PRESS fits easily in the middle ground between a repeat trabeculectomy and a larger glaucoma drainage device like a Baerveldt, Molteno, or an Ahmed tube shunt (Table 40.2).

The appeal of the EX-PRESS is that it provides for a more uniform, consistent, and reliable postoperative course than a standard trabeculectomy with the added benefit of rapid recovery. Maris et al. [4] in a retrospective comparative case series studied 49 eyes with the EX-PRESS and 47 eyes with a standard trabeculectomy. Success was defined as IOP $\geq$5 and $\leq$21 mmHg, with or without glaucoma medications, without further glaucoma surgery or removal of the implant. Early postoperative hypotony was defined as IOP <5 mmHg during the first postoperative week. The authors noted that although the mean IOP was significantly higher in the early postoperative period in the EX-PRESS group compared with the trabeculectomy group, the reduction of IOP was similar in both groups after 3 months. The number of postoperative glaucoma medications in both groups was not significantly different. Kaplan-Meier survival curve analysis showed no significant difference in success between the two groups (p=0.594). The success rate at an average of 11 months was 90 % for the EX-PRESS shunt compared to 92 % for trabeculectomies at last follow-up. The authors concluded that the EX-PRESS

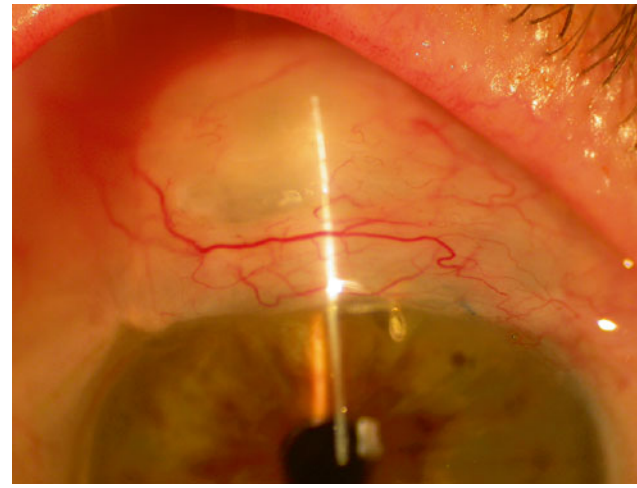

Fig. 40.10 There is often enough conjunctiva available between the side port vitrectomy scars to form a posterior bleb following a pars plana vitrectomy

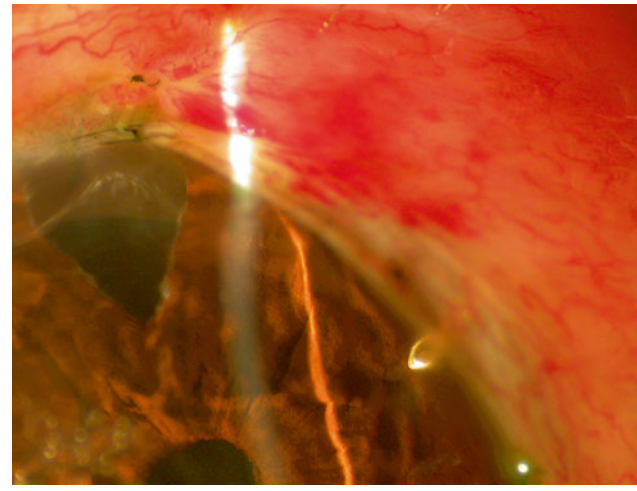

Fig. 40.11 One day following a nasal EX-PRESS insertion that avoided the original scarred superior conjunctiva

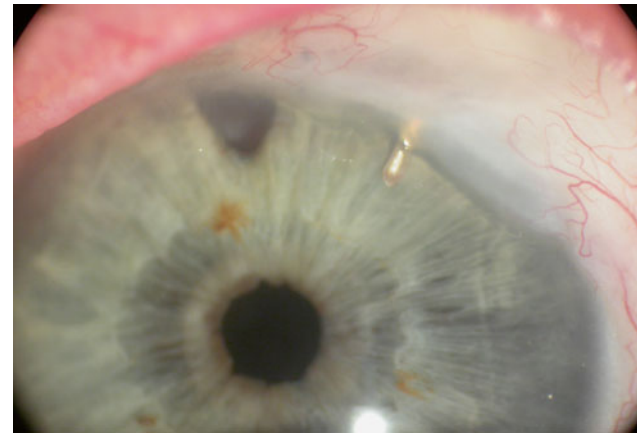

Fig. 40.12 A low diffuse bleb 2 years following an EX-PRESS shunt that was placed following a failed combined phacoemulsification-trabeculectomy. Note that an iridectomy is not needed with the EX-PRESS mini-shunt procedure

Table 40.2 Indications and contraindications for the EX-PRESS mini-shunt

EX-PRESS indications
Open-Angle Glaucoma refractory to medical and laser treatment
Open-Angle Glaucoma when a filtration procedure has failed
With combined glaucoma and cataract procedure—the EX-PRESS may have the advantage of faster visual recovery compared with trabeculectomy
Aphakic glaucoma—since there is no iridectomy required with the EX-PRESS implantation there is less risk of vitreous moving forward through a new iridectomy
Sturge-Weber syndrome—since choroidal effusions following trabeculectomy are high in this subset of patients; implantation of the EX-PRESS may offer a safer alternative because of its lower rate of prolonged postoperative hypotony [11]
EX-PRESS contraindications
Narrow Angle Glaucoma, unless the lens is removed
Congenital or juvenile glaucoma
Aniridia and anterior segment dysgenesis syndromes
Neovascular glaucoma
Microphthalmia

implant had similar IOP-lowering efficacy with a lower rate of early hypotony compared with trabeculectomy.

At the Wills Eye Institute, we retrospectively reviewed the data of 100 eyes of 100 patients who underwent placement of an EX-PRESS shunt under a scleral flap between March 2003 and October 2006 (mean follow-up 27 ± 13.2 months) [10]. IOP was reduced from a mean preoperative value of 27.7 ± 9.2 mmHg to a mean postoperative value of 14.0 ± 5.1 mmHg at last follow-up ($p < 0.0001$). The number or glaucoma medications decreased from a preoperative value of 2.7 ± 1.1 medications to 0.7 ± 1.0 medications at last follow-up. Postoperative complications were minimal, the most significant being uncontrolled IOP leading to failure. In this series, 83.7 % of the procedures were successful with or without medications. In those who had a prior cataract or failed trabeculectomy surgery, an EX-PRESS shunt was successful in 59.6 % and 65.3 %, respectively, after 3 years of follow-up.

There are few prospective studies comparing the EX-PRESS shunt to the trabeculectomy in the literature. In a single-surgeon prospective study, de Jong et al. [9] demonstrated higher success rates and fewer glaucoma medications in 78 eyes with the EX-PRESS shunt compared to trabeculectomy after 1–3 years of follow-up. However, after 4 and 5 years of follow-up, the difference in success rates and IOP were not statistically significant. In another single-surgeon prospective study, Dahan et al. [11] demonstrated similar IOP control with the EX-PRESS shunt and trabeculectomy after 1 and 2 years of follow-up. However, the EX-PRESS group required fewer glaucoma medications compared to the trabeculectomy group.

More recently, a prospective randomized controlled clinical trial comparing the effectiveness and safety of the EX-PRESS shunt and standard trabeculectomy has been published [12]. This study included a total of 120 eyes with 59 eyes treated with EX-PRESS and 61 eyes treated with trabeculectomy. Success was defined as $5 \leq \text{IOP} \leq 18$ mmHg without further glaucoma surgery. After 2 years of follow-up, the success rates were similar, being 83 % for the EX-PRESS and 79 % for the trabeculectomy group ($p = 0.563$). The mean intraocular pressure and number of glaucoma medications after 2 years of follow-up were also similar ($p = 0.927$ and $p = 0.383$ respectively). The visual acuity returned to baseline after 1 month in the EX-PRESS shunt group and after 3 months after trabeculectomy. More rapid recovery of vision after EX-PRESS shunt has been shown in a few other studies as well [13, 14]. It is hypothesized that the more rapid visual recovery may be due to decreased intraoperative time and inflammation due to the lack of sclerostomy and peripheral iridectomy with the EX-PRESS procedure. This study also demonstrated that the total number of postoperative complications was significantly higher after trabeculectomy than after EX-PRESS shunt implantation ($p = 0.013$) but it must be noted that the difference in complication rates is mainly due to a higher hyphema rate with trabeculectomies. Hyphemas are more likely to occur due to the peripheral iridectomy that is often performed during a standard trabeculectomy. All the hyphemas in this study were self-resolving.

Summary for the Clinician

- A multi-center randomized controlled trial comparing EX-PRESS vs. trabeculectomy with mitomycin-C found the two procedures equally efficacious in terms of IOP control and need for postoperative glaucoma medications; however, it appears that there is quicker visual recovery and a lower risk of hyphema with the EX-PRESS shunt.

40.5 How Does Surgical Technique Differ Between an EX-PRESS Shunt Procedure and a Trabeculectomy, and What Can Be Done to Obtain Better Outcomes with the Procedure?

The surgical technique for EX-PRESS implantation is similar to standard trabeculectomy. Both procedures work well with either a limbal or a fornix-based incision and both require a one-third to half thickness scleral flap. However during a trabeculectomy, a portion of the trabecular meshwork and cornea must be removed in order to establish a conduit through which aqueous can flow. In phakic eyes, an iridectomy is always necessary to prevent the iris from blocking the sclerostomy site in the event of chamber shallowing in the postoperative period.

The EX-PRESS shunt surgery differs in that neither a sclerostomy nor an iridectomy is required. Anterior segment surgeons may find the EX-PRESS a good alternative to standard filtration surgery since the fistula size of 50 μm is constant [15, 16]. In contrast, trabeculectomy flow may vary more widely from case to case depending on internal ostium size and tension of suture closure. The EX-PRESS shunt can be less traumatic compared to trabeculectomy and the other large glaucoma implants. Mark Sherwood et al. have shown that the levels of TGF-β are less in rabbits implanted with the EX-PRESS as compared to rabbits undergoing standard trabeculectomy [unpublished data], suggesting decreased inflammation following EX-PRESS implantation. It has also been suggested that the visual recovery with the EX-PRESS shunt may occur more quickly compared to trabeculectomy. This is especially important when performing combined cataract and glaucoma surgery, where the patient's expectation for immediate improvement of vision is high [17–19].

In order to increase the success of the EX-PRESS implantation, it is necessary to allow ample flow of aqueous through the posterior end of the scleral flap when the anterior chamber is inflated to an IOP of about 20 mmHg. In our practice, the one or two anterior releasable or laserable sutures are tied tightly and by 3 weeks postoperatively the releasable as well as the conjunctival sutures are removed (Fig 40.13). The

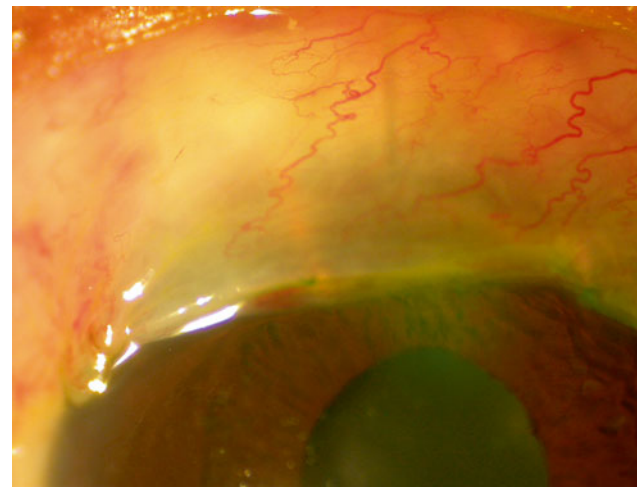

Fig. 40.13 At 1 week, IOP was 18 mmHg so a releasable suture was removed and IOP decreased to 9 mmHg. Microcysts are visible in the bleb. The conjunctival sutures are removed at 3 weeks post-op

sutures are removed at 3 weeks postoperatively as the conjunctiva should have adequately healed to the limbus at that point and to avoid any risk of infection or inflammation from the suture in the future. If the starting IOP is greater than 25–30 mmHg, it is advisable to fill the anterior chamber with a low molecular weight sodium hyaluronate to guard against hypotony.

Summary for the Clinician

- Neither a sclerostomy nor an iridectomy is needed with the EX-PRESS mini-shunt.
- Both the surgery itself and the postoperative course are more standardized and predictable than current trabeculectomy surgery since the flow through the device is always the same.
- It is recommended that either one or two sutures (either releasable or laserable) be placed anteriorly on the scleral flap to allow for posterior flow of aqueous toward the orbit.
- The anterior conjunctival sutures can be removed/cut around the third postoperative week once the incision is healed, but if an anterior wound leak is noted they should be left in place.

40.6 What Complications Are Specific to the EX-PRESS Shunt Procedure?

Complications typically seen with a trabeculectomy can also be observed following implantation of the EX-PRESS implant. Immediate postoperative hypotony, shallow or flat anterior chamber, hyphema, and choroidal detachments do occur, although to a lesser extent because of the small 50 μm drainage orifice [1, 15]. The usual directive on how to avoid these complications in other filtration procedures is also applicable to filtration surgery with the EX-PRESS. Unique complications to the EX-PRESS shunt have to do with placement of the device—it can end up in the iris if its entrance is to posterior or in the cornea if too anterior.

In terms of toxicity of the material, no adverse reports have been published to this date and the shunt is MRI compatible [20]. Moreover, interpretation of MRI scans of the orbit and brain is not affected by EX-PRESS shunt artifacts. There have been rare reports of erosion when inserted directly under the conjunctiva, and therefore this is no longer advisable [21]. It is possible to have the implant extrude after direct trauma [22] and the shunt when improperly placed can dislocate into the anterior chamber [23]. On occasion, the implant will need to be safely removed.

Glaucoma surgery is constantly evolving. The perfect glaucoma procedure has yet to be invented. However, the desire to minimize complications while maximizing outcomes continues to move surgical technology forward. Currently, the EX-PRESS P-50 appears to be an effective addition to our armamentarium to lower IOP in patients with refractory glaucoma [24].

Summary for the Clinician

- Complications common to trabeculectomy are also observed after the EX-PRESS shunt procedure, but to a lesser degree than with trabeculectomy. These include hyphema, hypotony, and choroidal detachment.
- Erosion of the device is extremely rare if placed under a scleral flap.

40.7 What Can I Do If My EX-PRESS Shunt Is Failing?

EX-PRESS shunts have not been shown to reduce the rates of surgical failure compared to the trabeculectomy [12]. Similar to the trabeculectomy, the most common cause of surgical failure is due to episcleral fibrosis. The rates of surgical failure are

lower with the use of anti-fibrotic agents such as mitomycin-C [25]. Sometimes, the shunt can become occluded by the iris or vitreous, causing elevation of IOP. This can sometimes be removed with a YAG laser on a low setting. Most of the time, however, the IOP rises due to bleb encapsulation or scarring. In these cases, one should first laser or release all scleral flap sutures. This is best done within the first postoperative month. One can also increase the frequency of steroid use and use aqueous suppressants to try to remodel the bleb. However, after all scleral sutures are removed and the IOP is still elevated, one can consider bleb needling with mitomycin-C. There are a few key differences in bleb needling after an EX-PRESS compared to after a standard trabeculectomy. First, the surgeon will not be able to enter the anterior chamber with the EX-PRESS shunt. Second, there is a risk of dislodging the shunt into the anterior chamber. Therefore, it is important to elevate the scleral flap by passing the needle parallel to the limbus rather than radial to the limbus [26].

Summary for the Clinician

- Management of the failing EX-PRESS shunt is similar to management of the failing trabeculectomy.
- One should ensure that there is no occlusion of the tube tip by vitreous, fibrin, or iris, which can be removed with a YAG laser on a low setting.
- Bleb needling with the EX-PRESS shunt can be performed with caution to avoid dislodging the shunt.

References

1. de Jong L. The Ex-PRESS glaucoma shunt versus trabeculectomy in open-angle glaucoma: a prospective randomized study. Adv Ther. 2009;26:336–45.
2. Nyska A, Glovinsky Y, Belkin M, Epstein Y. Biocompatibility of the Ex-PRESS miniature glaucoma drainage implant. J Glaucoma. 2003;12:275–80.
3. Mermoud A. Ex-PRESS implant. Br J Ophthalmol. 2005;89:396–7.
4. Maris PJG, Ishida K, Netland PA. Comparison of trabeculectomy with Ex-PRESS miniature glaucoma device implanted under scleral flap. J Glaucoma. 2007;16:14–9.
5. Wamsley S, Moster MR, Rai S, Alvim HS, Fontanarosa J. Results of the use of the Ex-PRESS miniature glaucoma implant in technically challenging, advanced glaucoma cases: a clinical pilot study. Am J Ophthalmol. 2004;138:1049–51.
6. Stewart RM, Diamond JG, Ashmore ED, Ayyala RS. Complications following ex-press glaucoma shunt implantation. Am J Ophthalmol. 2005;140:340–1.
7. Dahan E, Carmichael TR. Implantation of a miniature glaucoma device under a scleral flap. J Glaucoma. 2005;14:98–102.
8. Sarkisian SR. Use of an injector for the Ex-PRESS Mini Glaucoma Shunt. Ophthalmic Surg Lasers Imaging. 2007;38:434–6.
9. de Jong L, Lafuma A, Aguadé A-S, Berdeaux G. Five-year extension of a clinical trial comparing the EX-PRESS glaucoma filtration device and trabeculectomy in primary open-angle glaucoma. Clin Ophthalmol. 2011;5:527–33.
10. Lankaranian D, Razeghinejad MR, Prasad A, Fakhraie G, Freitas DJ, Ichhpujani P, Moster MR. Intermediate-term results of the Ex-PRESS miniature glaucoma implant under a scleral flap in previously operated eyes. Clin Experiment Ophthalmol. 2011;39:421–8.
11. Dahan E, Ben Simon GJ, Lafuma A. Comparison of trabeculectomy and Ex-PRESS implantation in fellow eyes of the same patient: a prospective, randomised study. Eye (Lond). 2012;26:703–10.
12. Netland PA, Sarkisian SR, Moster MR, Ahmed IIK, Condon G, Salim S, Sherwood MB, Siegfried CJ. Randomized, prospective, comparative trial of EX-PRESS glaucoma filtration device versus trabeculectomy (XVT study). Am J Ophthalmol. 2014;157:433–40.
13. Sugiyama T, Shibata M, Kojima S, Ueki M, Ikeda T. The first report on intermediate-term outcome of Ex-PRESS glaucoma filtration device implanted under scleral flap in Japanese patients. Clin Ophthalmol. 2011;5:1063–6.
14. Beltran-Agullo L, Trope GE, Jin Y, Wagschal LD, Jinapriya D, Buys YM. Comparison of visual recovery following Ex-PRESS versus trabeculectomy: results of a prospective randomized controlled trial. J Glaucoma. 2015;24(3):181–6.
15. Coupin A, Li Q, Riss I. Ex-PRESS miniature glaucoma implant inserted under a scleral flap in open-angle glaucoma surgery: a retrospective study. J Fr Ophtalmol. 2007;30:18–23.
16. Verbraak FD, de Bruin DM, Sulak M, de Jong LAMS, Aalders M, Faber DJ, van Leeuwen TG. Optical coherence tomography of the Ex-PRESS miniature glaucoma implant. Lasers Med Sci. 2005;20:41–4.
17. Rivier D, Roy S, Mermoud A. Ex-PRESS R-50 miniature glaucoma implant insertion under the conjunctiva

combined with cataract extraction. J Cataract Refract Surg. 2007;33(11):1946–52.
18. Traverso CE, De Feo F, Messas-Kaplan A, Denis P, Levartovsky S, Sellem E, Badalà F, Zagorski Z, Bron A, Gandolfi S, Belkin M. Long term effect on IOP of a stainless steel glaucoma drainage implant (Ex-PRESS) in combined surgery with phacoemulsification. Br J Ophthalmol. 2005;89(4):425–9.
19. Gandolfi S, Traverso CF, Bron A, Sellem E, Kaplan-Messas A, Belkin M. Short-term results of a miniature draining implant for glaucoma in combined surgery with phacoemulsification. Acta Ophthalmol Scand Suppl. 2002;236:66.
20. De Feo F, Roccatagliata L, Bonzano L, Castelletti L, Mancardi G, Traverso CE. Magnetic resonance imaging in patients implanted with Ex-PRESS stainless steel glaucoma drainage microdevice. Am J Ophthalmol. 2009;147:907–11.
21. Tavolato M, Babighian S, Galan A. Spontaneous extrusion of a stainless steel glaucoma drainage implant (Ex-PRESS). Eur J Ophthalmol. 2006;16:753–5.
22. Garg SJ, Kanitkar K, Weichel E, Fischer D. Trauma-induced extrusion of an Ex-PRESS glaucoma shunt presenting as an intraocular foreign body. Arch Ophthalmol. 2005;123:1270–2.
23. Teng CC, Radcliffe N, Huang JE, Farris E. Ex-PRESS glaucoma shunt dislocation into the anterior chamber. J Glaucoma. 2008;17:687–9.
24. Hendrick AM, Kahook MY. Ex-PRESS mini glaucoma shunt: surgical technique and review of clinical experience. Expert Rev Med Devices. 2008;5:673–7.
25. Fontana H, Nouri-Mahdavi K, Caprioli J. Trabeculectomy with mitomycin C in pseudophakic patients with open-angle glaucoma: outcomes and risk factors for failure. Am J Ophthalmol. 2006;141:652–9.
26. Freidl KB, Moster MR. ExPRESS shunt surgery: preferred glaucoma surgery in residency training? Surv Ophthalmol. 2012;57:372–5.

Procedural Treatments: Phacotrabeculectomy

41

Héctor Javier Fontana

Core Messages

- There are multiple ways to handle simultaneous glaucoma and cataract.
- Trabeculectomy provides better IOP control than phacotrabeculectomy, which provides better IOP control than cataract extraction alone.
- Trabeculectomy increases the incidence of visually significant cataract.
- Premium lens implants can be considered in select cases.

41.1 Under What Circumstances Should a Combined Phacotrabeculectomy Be Performed?

The management of simultaneous glaucoma and cataracts, either with a combined or staged procedure, raises a number of questions. According to Jampel and colleagues, many of the questions lack a good answer, as the literature on this topic is scant. Some key unanswered questions are (1) which procedure (trabeculectomy followed by cataract extraction at another time vs. simultaneous procedures) achieves a larger reduction in intraocular pressure (IOP), (2) how many eyes undergoing trabeculectomy will eventually require cataract extraction, and (3) how is the quality of life affected by the two approaches [1]. Also important to keep in mind is that the trend towards combined vs. separate procedures has varied over the decades with the introduction of new techniques. The trend now tends toward separate surgeries.

41.1.1 When Should I Add a Trabeculectomy to Cataract Surgery?

Combining glaucoma surgery and cataract extraction should be considered in patients in whom there is a functionally significant cataract and less than ideal IOP control. Cataract extraction alone has been shown to lower IOP in glaucoma patients [2]. The exact mechanism of this IOP drop is unknown, and one cannot predict which individual patient will enjoy an IOP reduction or the magnitude of the reduction. In a literature review, Friedman and colleagues found long-term IOP reduction of 2–4 mmHg by extracapsular cataract extraction or phacoemulsification alone and they found that the evidence was weak [3].

Some patients may suffer significant IOP elevations in the early postoperative period following

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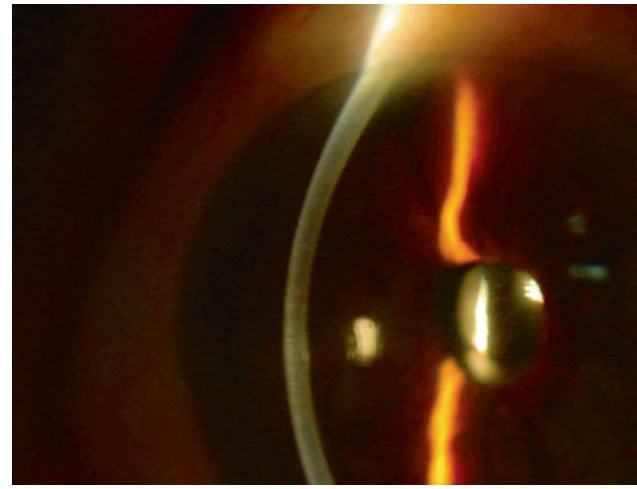

Fig. 41.1 Phacotrabeculectomy: two-site approach

uncomplicated cataract surgery, especially if rabecular meshwork outflow is significantly compromised. These IOP spikes can reach very high levels and pose a significant threat to vision in patients with preexisting glaucomatous vision loss [4–6]. Patients with visually significant cataract who cannot afford an IOP spike, is on more than two topical medications, is intolerant to current medications, is having trouble complying with the recommended drop regimen, or for whom a second trip to the operating room is extremely difficult medically, socially, or economically, are those for whom a combined phacotrabeculectomy should be considered [7, 8] (Fig. 41.1).

The evidence is strong that IOP reduction is greater over the long term with combined cataract extraction and trabeculectomy than with cataract extraction alone [3]. Those undergoing combined procedures on average will have an IOP 3–4 mmHg lower than those undergoing cataract extraction alone and will be using fewer medications over long-term follow-up. The combined procedure also reduces the frequency of early postoperative IOP spikes, although it does not eliminate them completely [9].

41.1.2 When Should I Add Phacoemulsification to a Trabeculectomy?

Another situation in which a combined phacotrabeculectomy may be considered is in a patient who needs a trabeculectomy but who also has a significant cataract. Glaucoma surgery substantially increases the risk for cataract or its progression in cases of preexisting cataracts [10, 11]. Eyes with glaucoma may develop cataracts at a different rate than normal eyes due to factors directly and indirectly related to their glaucoma. After median follow-up of 7.7 years in the Collaborative Initial Glaucoma Treatment Study, patients randomized into the surgical arm of the study had a threefold increased risk of requiring cataract extraction over 5 years compared to the medically treated patients [12]. Sixty-one percent of trabeculectomy first patients went on to cataract extraction vs. 47 % of medication first patients. Glaucoma medications themselves may also increase the risk of cataracts [13]. The increased incidence appears to be related to changes in aqueous humor dynamics that topical hypotensive medications and surgery induce [14, 15].

The small incision clear-corneal cataract surgery techniques and foldable intraocular lenses in use today create less inflammation and damage to the conjunctiva and sclera than extracapsular techniques of a few decades ago. Compared to extracapsular cataract extraction, the small incision procedures have considerably improved long-term IOP control in combined cases [1, 16, 17]. Likewise, the use of antimetabolites has similarly improved success rates of phacotrabeculectomy.

When it comes to the published literature and my own experience in the management of patients with both conditions, combined surgery should be performed in patients with coexistent visually significant cataract and glaucoma on maximally tolerated medical treatment, especially when a significant postoperative IOP spike would be dangerous to the eye [7, 8]. This may include patients who demonstrate poor compliance with prescribed treatment or those with contraindications to additional medications [8, 9]. Finally, it is important to consider that a combined procedure entails greater comfort and an economic advantage over two separate surgeries [8].

Summary for the Clinician

- IOP response is often unpredictable after cataract surgery alone in glaucomatous eyes.
- Dangerous IOP spikes may occur after uncomplicated phacoemulsification.
- Long-term IOP reduction is greater after phacotrabeculectomy than after phacoemulsification alone.
- Consider phacotrabeculectomy in a cataract patient who cannot tolerate an IOP spike, is intolerant to medications, is nonadherent with medication, or on multiple medications.
- Glaucoma surgery alone increases the risk of cataract.
- Consider phacotrabeculectomy in the glaucoma patient needing a trabeculectomy who has a visually significant cataract for whom one surgery may offer economic and social advantages.

41.2 Under What Circumstances Should a Phacotrabeculectomy Not Be Performed?

This question can also be answered in two ways. One is from the standpoint where glaucoma is the primary problem. The other standpoint is where the cataract is the primary problem.

41.2.1 Glaucoma as the Primary Problem

A number of case series and retrospective studies indicate that trabeculectomy alone provides better IOP control than a combined phacotrabeculectomy. In a comparative study on Caucasian patients undergoing either trabeculectomy or phacotrabeculectomy, IOP control at 1 year was better in the trabeculectomy alone group [18]. Park et al. retrospectively compared 40 patients undergoing 5-FU trabeculectomy to 40 patients undergoing 5-FU phacotrabeculectomy. The trabeculectomy group had a significantly lower IOP than the combined group, −10.3 vs. −6.8 mmHg [19]. A third study by Chang et al. reports that combined surgery is just as effective at reaching success (defined as IOP ≤ 16 mmHg on no drops) as trabeculectomy alone; however, more postoperative interventions, i.e., 5-FU injections, were necessary in the phacotrabeculectomy group in an effort to reach success [20], and this finding was attributed to more pronounced scarring of the bleb in the combined group. Of note, the magnitude of IOP reduction was greater in the trabeculectomy alone group—44.6 % vs. 31.2 %.

If a patient is in need of very low IOP and does not have a significant cataract, a trabeculectomy by itself is the best procedure. If the patient also has a significant cataract, then questions the surgeon should ask himself/herself is how low does the IOP need to be, what kind of results have I personally had in the past with combined procedures and separate procedures, and what kind of hardship would it be to the patient to have a staged procedure. One report in the literature shows that the effect on long-term IOP control of subsequent phacoemulsification following trabeculectomy is minimal [19].

41.2.2 Cataract as the Primary Problem

If a patient's primary problem is a visually significant cataract and the glaucoma is well controlled on a small number of topical hypotensive drugs, then phacoemulsification performed alone, aimed

at optimizing the patient's vision, is probably the best option.

Recent published data showed that patients included in OHTS who underwent cataract surgery alone had significantly lower postoperative IOPs (mean postop 19.8 ± 3.2 mmHg vs. mean preop 23.9 ± 3.2 mmHg). Additionally, the postoperative IOP remained lower than the preoperative IOP for at least 36 months [21].

To evaluate whether or not to perform combined surgery, questions to ask are (1) how many medications is the patient on already (many people will perform a phacotrabeculectomy if the answer is three or more), (2) would the patient be able to tolerate an IOP spike after cataract extraction [7, 8], (3) is the patient having trouble with adherence and persistence to his/her drug regimen or side effects [8, 9], and (4) is there an advantage in taking the patient to the operating room only once [8].

Summary for the Clinician

- Trabeculectomy alone should be considered in patients who require very low IOP postoperatively where vision is threatened mainly by inadequate control of IOP.
- Phacoemulsification alone should be performed when visual impairment is mainly due to cataract and the IOP is under adequate medical control on a small number of medications.

41.3 How Is the Postoperative Course of a Phacotrabeculectomy Different Than That After the Individual Surgeries?

41.3.1 Postoperative Course of a Phacotrabeculectomy vs. Trabeculectomy Alone

When a phacotrabeculectomy is performed there may be increased and prolonged inflammation compared to that seen after trabeculectomy alone due to a longer period of globe manipulation and release of lens proteins [22]. In an analysis of anterior chamber flare in individuals undergoing trabeculectomy vs. phacoemulsification, Siriwardena et al. published that flare levels remained significantly above baseline up to 3 months post phacoemulsification, whereas they returned to baseline within 4 weeks in the trabeculectomy group [23]. The authors attributed this finding to a higher release of lens epithelium and proteins into the aqueous humor, to the ultrasound effect, and the high volume of liquid flowing through the eye during phacoemulsification. These factors can increase the production of cytokines in the aqueous humor that stimulate the scarring process.

Whether to perform a limbus or fornix based conjunctival wound in phacotrabeculectomy is another common question. Similar long-term results are seen after either type of incision [24–26]. Although a fornix-based trabeculectomy allows better visualization during one-site cataract surgery, it is also associated with a higher risk of wound leakage. Generally after cataract surgery, a water-tight wound is desirable to decrease the risk of endophthalmitis. Of note, the trabeculectomy will lower eye pressure allowing the clear corneal wound to gape. In order to minimize this risk, corneal wounds should be sutured in combined two-site cases. Hypotony leading to shallow chambers can occur after phacotrabeculectomy, although the lens implant takes up less volume than a natural lens does and therefore lens-corneal touch is less likely to occur. The use of releasable sutures constitutes an option to avoid hypotony in the early postoperative period (Fig. 41.2).

41.3.2 Postoperative Course of a Phacotrabeculectomy vs. Phacoemulsification Alone

Visual recovery may be more prolonged with a greater incidence of postoperative refractive error following phacotrabeculectomy. It has been published that after phacotrabeculectomy, complete visual recovery may take up to 6 vs. 1 or 2 weeks at most with phacoemulsification

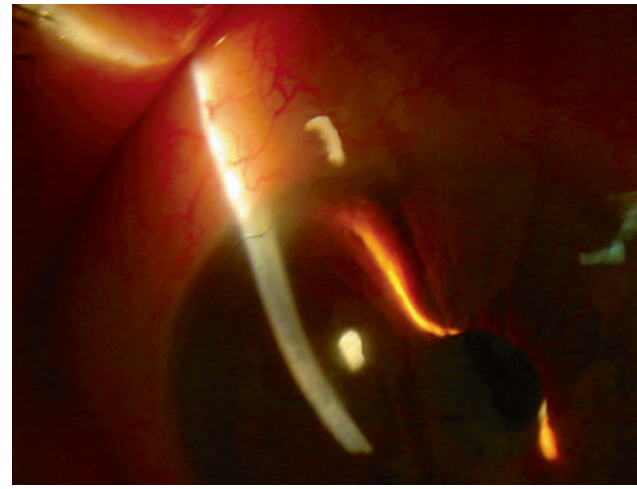

Fig. 41.2 Phacotrabeculectomy: two-site approach associated with releasable sutures

alone. Chan et al. retrospectively evaluated the refraction of patients subjected to phacotrabeculectomy vs. phacoemulsification and found myopic refractive errors are more common after phacotrabeculectomy. The authors speculated that myopia was due to shallowing of the anterior chamber in a soft eye [27].

Usually combined cataract and glaucoma surgery is accompanied by a higher risk of intra and postoperative complications. Many of the complications associated with phacoemulsification may be particularly accentuated in a combined surgery and may relate to increased inflammation, added surgical manipulation, wound integrity, and the presence of lens proteins associated with the cataract portion of the surgery [21].

Summary for the Clinician

- Following phacotrabeculectomy, there is increased inflammation compared to trabeculectomy alone.
- Following phacotrabeculectomy, the postoperative course may be less predictable than after phacoemulsification alone (i.e., refractive errors).
- There may be an increased rate of intraoperative and postoperative complications following phacotrabeculectomy.

41.4 What Lens Implants Can Be Used in a Glaucoma Patient?

Surgeons should carefully discuss IOL selection and refractive options in patients who have cataract and glaucoma. Monofocal, multifocal, accommodative, and toric intraocular lens implants (IOLs) have all been implanted into glaucomatous eyes. However, there are circumstances where some of these lenses may be contraindicated. Glaucomatous eyes have a number of issues that influence which type of implant is indicated [28]. In general, any abnormality of the optic nerve that restricts potential visual acuity, contrast sensitivity, color perception, or visual field [29, 30] may be considered a relative contraindication to multifocal IOLs.

A patient with cataracts and glaucoma has decreased functional vision (including visual acuity, visual field, color perception, and contrast sensitivity [42]) due to both diseases. Defects attributed to cataracts are reversible, unlike those of glaucoma. Taking this into account, it is reasonable to consider the following groups as potential candidates for premium IOL implantation [43, 44].

1. Patients with suspected glaucoma or with ocular hypertension without optic nerve and visual field damage who are well monitored and stable.

2. Glaucomatous patients with mild defects in the visual field who are well monitored and stable.
3. Patients with a similar level of glaucoma in both eyes that is not severe, advanced, or progressive.

One issue to consider is how glaucoma affects the final refractive status of the eye. Trabeculectomy may induce astigmatism and axial length/anterior chamber depth changes. Multifocal lenses are less tolerant of low ametropia than monofocal lenses, and in most cases require emmetropia [45]. Apart from the decrease in contrast sensitivity, this is another reason for advising against multifocal lens implantation in patients with glaucoma.

Zonular weakness also plays an important role in the consideration of premium lens in a glaucoma patient for two reasons:

– Performance of multifocal lenses is very sensitive to any decentration.
– Implantation of aspheric lenses is advised in patients with glaucoma as it compensates partially for the loss of contrast sensitivity. But, aspheric lenses decentered over 0.5 mm increase aberrations rather than decreasing them. They are not advised if there is any risk of decentration of the capsular bag.

While some authors believe that there is a contraindication to implanting multifocal intraocular or toric lenses in patients with glaucoma if they have zonular weakness, others do not see any inconvenience for their implantation as long as the capsular bag is correctly supported (Eye World September 2011).

41.4.1 Multifocal IOLs

Multiple studies show the efficacy of multifocal lenses in providing better uncorrected near and intermediate visual acuity compared to monofocal lenses, with a similar level of distance visual acuity [31–33]. Diffractive multifocal lenses are based on the Huygens-Fresnel principle [34], presenting concentric rings that result in two or more coexisting retinal images. These IOLs provide very good reading and distance visual acuity and are independent of pupil size. Refractive multifocal lenses provide excellent intermediate and distance visibility. Near visual acuity is typically adequate but may not be sufficient to see very small print, such as phonebook entries or medication labels, and depends on pupil size [35]. Diffractive and refractive multifocal IOLs produce similar uncorrected distance visual acuity, but the former provides better uncorrected near visual acuity [36–39], resulting in a higher spectacle independence.

Reports of photic episodes (glare, halos at night), variable loss of clarity, and low contrast acuity have been reported by patients with multifocal IOLs, creating patient dissatisfaction. Lower contrast sensitivity becomes more clinically relevant in patients with decreased contrast sensitivity due to ocular pathology (i.e., glaucoma).

41.4.2 Accommodative IOLs

An accommodative IOL is able to provide vision at multiple distances, in a mechanism similar to the natural, crystalline lens. An accommodative lens implant moves inside the eye as the eye's focusing muscle contracts, mimicking the eye's natural ability to focus. This feature addresses distance, intermediate and near vision and makes the recipient less dependent on glasses or contact lenses.

These IOLs have some advantages compared to multifocal lenses: they act like monofocal lenses but, they provide better visual acuity for intermediate and near vision. Additionally, they do not depend on pupil size, provide less dysphotopic effects and do not decrease contrast sensitivity. However, they have some disadvantages: variability of the postoperative outcome; the need for further correction for near vision; higher risk for capsular contraction and opacification [40]. These lenses are contraindicated in the presence of weak zonules, such as in pseudoexfoliation glaucoma.

41.4.2.1 Toric IOLs

Patients who have some degree of corneal astigmatism before cataract surgery usually need glasses or contact lenses after surgery. To overcome this limitation, toric IOLs were developed to precisely correct astigmatism [41]. Even though, they can be successfully used after filtration surgery, they are relatively contraindicated in a combined procedure because the postoperative corneal astigmatism may be difficult to predict.

Summary for the Clinician

- Poor contrast sensitivity, induced astigmatism, capsular decentration, and zonular weakness are issues that have to be anticipated in glaucomatous eyes undergoing cataract surgery because they will affect IOL selection.

References

1. Jampel H, Friedman D, Lubomski L, et al. Effect of technique on intraocular pressure after combined cataract and glaucoma surgery: an evidence-based review. Ophthalmology. 2002;109:2215–24.
2. Kim D, Doyle J, Smith M. Intraocular pressure reduction following phacoemulsification cataract extraction with posterior chamber lens implantation in glaucoma patients. Ophthalmic Surg Lasers. 1999;30:37–40.
3. Friedman D, Jampel H, Lubomski L, et al. Surgical strategies for coexisting glaucoma and cataract: an evidence-based update. Ophthalmology. 2002;109:1902–15.
4. Rich W, Cohan B. Early ocular hypertension after cataract extraction. Br J Ophthalmol. 1974;58:725–31.
5. Shields M. Combined cataract extraction and glaucoma surgery. Ophthalmology. 1989;89:231–7.
6. Shields M. Combined cataract extraction and guarded sclerectomy: reevaluation in the extracapsular era. Ophthalmology. 1986;93:366–70.
7. Krupin T, Feitl M, Bishop K. Postoperative intraocular pressure rise in open angle glaucoma patients after cataract or combined cataract-filtration surgery. Ophthalmology. 1989;96:579–84.
8. Storr-Paulsen A, Bernth-Petersen P. Combined cataract and glaucoma surgery. Curr Opin Ophthalmol. 2001;12:41–6.
9. Storr-Paulsen A, Laugesen C. A prospective study of combined phacoemulsification-trabeculectomy versus conventional phacoemulsification in cataract patients with coexisting open angle glaucoma. Acta Ophthalmol. 1998;76:696–9.
10. Hylton C, Friedman D, et al. Cataract after filtration surgery. Am J Ophthalmol. 2003;135:231–2.
11. Investigators AGIS. The Advanced Glaucoma Intervention Study: 8. Risk of cataract formation after trabeculectomy. Arch Ophthalmol. 2001;119:1771–9.
12. Lichter P, Musch D, Gillespie B, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108:1943–53.
13. Chandrasekaran S, Rochtchina E, Mitchell P. Associations between elevated intraocular pressure and glaucoma, use of glaucoma medications, and 5-year incident cataract: The Blue Mountains Eye Study. Ophthalmology. 2006;113:417–24.
14. Verges C, Cazal J, Lavin C. Surgical strategies in patients with cataract and glaucoma. Curr Opin Ophthalmol. 2005;16:44–52.
15. Lee R. Surgical management of coexisting cataract and glaucoma. Int Ophthalmol Clin. 2004;44:151–66.
16. Wishart P. Combined cataract extraction and trabeculectomy: phacoemulsification compared with extracapsular technique. Ophthalmic Surg Lasers. 1993;24:814–21.
17. Shingleton B, Kuperwaser M. Comparison of combined cataract and glaucoma surgery using planned extracapsular and phacoemulsification techniques. Ophthalmic Surg Lasers. 1995;26:414–9.
18. Lochhead J, Salmon J. Long term effect on intraocular pressure of phacotrabeculectomy compared to trabeculectomy. Br J Ophthalmol. 2003;87:850–2.
19. Park H, Caprioli J. Temporal corneal phacoemulsification combined with superior trabeculectomy. A retrospective case-control study. Arch Ophthalmol. 1997;115:318.
20. Chang L, Thiagarajan M, Moseley M, et al. Intraocular pressure outcome in primary 5FU phacotrabeculectomies compared with 5FU trabeculectomies. J Glaucoma. 2006;15:475–81.
21. Mansberger SL, Ocular Hypertension Treatment Study Group. Reduction in intraocular pressure after cataract extraction: the Ocular Hypertension Treatment Study. Ophthalmology. 2012;119(9):1826–31.
22. Heffelfinger B, Berman M, Krupin T, et al. Surgical management of coexisting glaucoma and cataract. Ophthalmol Clin North Am. 2000;13:545–51.
23. Siriwardena D, Minassian D, Dart J, et al. Anterior chamber flare after trabeculectomy and after phacoemulsification. Br J Ophthalmol. 2000;84:1056–7.
24. Lemon L, Shin D, Kim C, et al. Limbus-based vs fornix-based conjunctival flap in combined glaucoma and cataract surgery with adjunctive mitomycin C. Am J Ophthalmol. 1998;125:340–5.
25. Shingleton B, O'Donoghue M, et al. Phacotrabeculectomy: limbus-based versus fornix-based conjunctival flaps in fellow eyes. Ophthalmology. 1999;106:1152–5.

26. Tezel G, Kass M, et al. Comparative results of combined procedures for glaucoma and cataract: II: limbus-based versus fornix-based conjunctival flaps. Ophthalmic Surg Lasers. 1997;28:551–7.
27. Chan J, Lai J, Tham C. Comparison of postoperative refractive outcome in phacotrabeculectomy and phacoemulsification with posterior chamber intraocular lens implantation. J Glaucoma. 2006;15:26–9.
28. Paletta Guedes RA, Paletta Guedes VM, Aptel F. Multifocal, toric, and aspheric intraocular lenses for glaucoma patients. J Fr Ophtalmol. 2011;34:387–91.
29. Duke-Elder S, Scott GI. Neuro-ophthalmology. In: Duke-Elder S, editor. System of ophthalmology, vol. XII. London: Kimpton; 1971. p. 11–5.
30. Miller NR. Walsh and Hoyt's clinical neuro-ophthalmology. 4th edition. Baltimore: Williams & Wilkins, Vol. 1; 1985. p. 212–25, 329–42.
31. Alió JL, ElKady B, Ortiz D, et al. Clinical outcomes and intraocular optical quality of a diffractive multifocal intraocular lens with asymmetrical light distribution. J Cataract Refract Surg. 2008;34:942–8.
32. Zelichowska B, Rekas M, Stankiewicz A, et al. Apodized diffractive versus refractive multifocal intraocular lenses: optical and visual evaluation. J Cataract Refract Surg. 2008;34:2036–42.
33. Alió JL, Tavolato M, De La Hoz F, et al. Near vision restoration with refractive lens exchange and pseudoaccommodating and multifocal refractive and diffractive intraocular lenses; comparative clinical study. J Cataract Refract Surg. 2004;30:2494–503.
34. Fresnel A. Memoire Sur un Nouveau Systeme d'Eclairage des Phares. Imprimerie Royale Paris, France, 29 juillet 1822.
35. Chian PJ, Chan JH, Haider SI, et al. Multifocal IOLs produce similar patient satisfaction levels. J Cataract Refract Surg. 2007;33:2057–61.
36. Peposee JS, Qazi MA, Davies J, et al. Visual performance of patients with bilateral vs combination Crystalens, Rezoom, and ReSTOR intraocular lens implants. Am J Ophthalmol. 2007;144:347–57.
37. Mester U, Hunold W, Wesendahl T, et al. Functional outcomes after implantation of Tecnis ZM900 and Array SA40 multifocal intraocular lenses. J Cataract Refract Surg. 2007;33:1033–1040.
38. Javitt JC, Steinert RF. Cataract extraction with multifocal intraocular lens implantation: a multinational clinical trial evaluating clinical, functional, and quality-of-life out-comes. Ophthalmology. 2000;107:2040–8.
39. Martinez-Palmer A, Gomez-Faina P, Espana-Albelda A, et al. Visual function with bilateral implantation of monofocal and multifocal intraocular lenses: a prospective, randomized, controlled clinical trial. J Refract Surg. 2008;24:257–64.
40. Moore RL, de Rojas Silva V, Mendicute del Barrio J. Multifocal lenses in glaucoma patients. J Emmetropia. 2012;3:31–42.
41. Mendicute J, Irigoyen C, Aramberri J, Ondarra A, Montes-Mico R. Foldable toric intraocular lens for astigmatism correction in cataract patients. J Cataract Refract Surg. 2008;34(4):601–7.
42. Gibelalde A, Mendicute J. Manifestaciones visuales en los pacientes con cataratas. In: Lorente R, Mendicute J, editors. Cirugía del cristalino. Ponencia Oficial de la Sociedad Española de Oftalmología, 2008. Madrid: MacLine S.L.; 2008. p. 205–13.
43. Kumar V, Phillips R, Prasad S. Multifocal intraocular lenses in the setting of glaucoma. Curr Opin Ophthalmol. 2007;18:62–6.
44. Teichman JC, Ahmed IK. Intraocular lens choices for patients with glaucoma. Curr Opin Ophthalmol. 2010;21:135–43.
45. Hayashi K, Manabe S, Yoshida M, Hayashi H. Effect of astigmatism on visual acuity in eyes with a diffractive multifocal intraocular lens. J Cataract Refract Surg. 2010;36:1323–9.

Procedural Treatments: Surgery in End-Stage Glaucoma

42

Fotis Topouzis and Panayiota Founti

Core Messages

- End-stage glaucoma requires stricter monitoring and quicker treatment decisions.
- Target intraocular pressure in end-stage glaucoma is in the lower teens. Clinical practice suggests that in some patients it may be even lower.
- Trabeculectomy and glaucoma drainage implants effectively reduce intraocular pressure in end-stage glaucoma patients and are generally considered to be safe. The risk of vision loss following glaucoma surgery may result from explainable visually devastating complications, such as hypotony maculopathy and endophthalmitis.
- The "wipe-out" phenomenon describes an immediate postoperative unexplained visual loss and is, at most, a rare phenomenon.

42.1 Should I Operate on a Patient with End-Stage Glaucoma?

42.1.1 First, What Is End-Stage Glaucoma?

End-stage glaucoma is a term used to describe glaucoma that has reached a stage of extreme or nearly total visual loss. Overall, end-stage glaucoma definition relies on the severity of visual impairment. However, there is no universally accepted definition. A commonly used criterion is a very constricted visual field (VF), less than 10 degrees diameter around central fixation. [1]. In the Advanced Glaucoma Intervention Study (AGIS), an AGIS VF score of 17–20 was used to classify an eye in the end-stage glaucoma group [2]. Others define end-stage glaucoma based on a visual acuity (VA) of 20/200 or worse, attributable to glaucoma [3].

42.1.2 What Are the Challenges in End-Stage Glaucoma?

Although peripheral vision is seriously affected in end-stage glaucoma, patients may maintain good central vision. Even with a visual acuity characterizing them as legally blind, it is possible for patients to perform simple daily tasks [4]. Therefore, the preservation of this remaining

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vision is of major importance. However, this is difficult to achieve because advanced visual field loss in itself increases the risk of further progression and blindness [5–7]. In addition, these patients face socioeconomic challenges that must be taken into account, such as being stigmatized and underemployed, as well as psychological challenges, including anxiety, fear or even hopelessness [8].

Obtaining reliable VF results in end-stage glaucoma patients may be quite difficult or in some cases impossible. When there is only a central island of vision and a VF test can be performed, a central 10-2 program may be more informative than 24-2 or 30-2 programs [9]. End-stage glaucoma patients need stricter monitoring and time-sensitive treatment decisions. The "wait and see" approach used in many glaucoma patients is a luxury that cannot be used in end-stage glaucoma patients. Even small changes may be functionally significant and these changes are difficult to differentiate from inter-test fluctuation [10]. Further, it is difficult to assess changes in an optic disc with severe glaucomatous damage. In end-stage glaucoma small changes in optic disc rim correspond to disproportionately significant changes in the VF, indicating decreased value of optic disc examination in assessing progression at this stage [11].

With regard to treatment, IOP reduction remains the only validated management approach to prevent glaucoma progression [12, 13]. According to the AGIS, an IOP in the lower teens is required to prevent progression in advanced glaucoma [14]. Medical treatment alone may not be enough to achieve such low target pressures.

42.1.3 When Should the Clinician Consider Surgery in End-Stage Glaucoma?

There is consensus agreement that glaucoma surgery is indicated when medical therapy is not available, not complied with, or not sufficiently effective in lowering IOP [15]. The more pronounced the damage and the greater the threat to central vision, the lower the IOP requirements and thus the lower the threshold for suggesting glaucoma surgery [15]. In the case of unreliable VFs or inability to perform VF examination, a decrease in visual acuity or a patient's perception of deterioration may be critical in the decision for surgical intervention, as there is a strong association between some types of perceived visual disability and the severity of binocular field loss [16].

Complete information on IOP through a daily curve may help the physician assess whether IOP is held within the desirable limits [17]. To prevent progression, IOP needs to be consistently low [18]. Large IOP fluctuation has been suggested as one of the strongest risk factors for glaucoma progression [14, 19–22] although there is controversy in the literature regarding this issue [23, 24]. Trabeculectomy has been associated with less diurnal IOP fluctuation compared to medical therapy in patients with advanced glaucoma [25, 26].

Using a variety of definitions, it has been estimated that 10–38 % of patients with OAG have advanced VF loss at diagnosis in at least one eye [5, 27, 28]. Even in cases of advanced VF loss the standard of care is to offer glaucoma surgery when medical therapy is not available, not complied with, or not sufficiently effective in lowering IOP [15]. However, the UK National Institute for Health and Care Excellence (NICE) guidelines suggest that patients who present with advanced glaucoma should be offered primary glaucoma surgery [29]. A systematic review on primary medical vs. surgical treatment for glaucoma concluded that there are no studies comparing modern medical treatment against modern surgical interventions in patients presenting with advanced disease and that this should be the objective of a randomized controlled trial (RCT) [30].

42.1.4 What Type of Surgery Is Appropriate for End-Stage Glaucoma?

Based on current evidence, trabeculectomy with antifibrotic agents is the incisional procedure of choice in eyes which have not had prior surgery, and combined procedures are less likely to be successful for IOP reduction compared to trabeculectomy alone [15]. Since its first description

in the late 1960s by Cairns [31] and Watson [32], trabeculectomy has undergone a number of modifications, including the use of releasable sutures [33, 34] and laser suture lysis [35] to regulate flow postoperatively, the use of mytomycin C to prevent scarring [36], and the "safer surgery system" [37]. Using these refinements success rates of at least 70 %, defined as IOP ≤18 mmHg, and of at least 60 %, defined as IOP ≤15 mmHg, with or without adjunctive IOP-lowering treatment have been reported 2–4 years after surgery [38, 39]. These results are predominantly seen in Caucasian patients with various stages of glaucoma. High rates of success have also been reported in African Caribbean patients [40]. Studies that have evaluated the outcomes of modern trabeculectomy specifically in advanced or end-stage glaucoma also suggest that trabeculectomy can effectively reduce IOP in this subgroup of patients [41–46].

Alternatively, aqueous shunts (which is the term preferred by the American National Standards Institute [47] to describe glaucoma drainage devices) have been generally reserved for cases in which glaucoma filtration surgery has failed or cases of refractory glaucomas (neovascular, uveitic, other secondary open-angle and angle-closure glaucomas), which do not respond well to standard filtration surgery [48]. The Tube vs. Trabeculectomy (TVT) study, which is a large RCT comparing 350-mm^2 Baerveldt glaucoma implant to trabeculectomy with mitomycin C in eyes with previous trabeculectomy and/or cataract extraction, found similar IOP reduction with both procedures after 5 years [49]. According to a report by the American Academy of Ophthalmology, indications for shunts have broadened as there is level I evidence that aqueous shunts are comparable with trabeculectomy for IOP control and duration of benefit [48]. On the other hand, the results of the TVT study require careful interpretation [50]. The frequency of complications of trabeculectomy in the TVT study is significantly higher compared to anecdotal results and previously published data [50, 51]. In addition, the outcomes of aqueous shunts have not been assessed in patients specifically with end-stage glaucoma.

With regard to other surgical options, nonpenetrating surgical (NPS) procedures are less effective in reducing IOP compared to trabeculectomy [52]. For this reason, they are not preferred in end-stage glaucoma, which usually requires IOP levels in the lower teens [14]. Similarly, emerging surgical techniques and devices for IOP reduction (the Fugo blade, Ex-PRESS mini glaucoma shunt, SOLX Gold Shunt, excimer laser trabeculotomy, canaloplasty, trabeculotomy by internal approach and trabecular micro-bypass stent) are not preferred in patients with end-stage glaucoma, because, based on the current state of evidence, no conclusions can be drawn on how these perform compared to trabeculectomy [53].

Cycloablation, including diode laser transscleral cyclophotocoagulation (TCP) or cyclocryotherapy, may be used in the treatment of glaucoma although side effects seem to be significantly lower with the former compared to the latter [54, 55]. Cycloablation has been conventionally used in those refractory cases in which all other treatments have failed, including incisional surgeries, or to prevent eyes with already very poor visual function from becoming painful [56]. Recent studies suggest that TCP could be used as an alternative approach to incisional surgery in the treatment of primary open-angle, pseudoexfoliative, and angle-closure glaucoma [57–59]. Also, there is some evidence that endoscopic cyclophotocoagulation (ECP), which is most commonly performed in conjunction with cataract surgery, may be an effective surgical option for moderate to advanced glaucoma [56, 60].

Furthermore, the physician should take into account that patients with end-stage glaucoma are likely to have undergone previous operations and/or to have used combinations of antiglaucoma drops for a long time. Both these factors may have a negative effect on the conjunctiva and on the outcome of a new operation [61, 62]. In view of the risks of a surgical procedure and their possible impact on an eye with end-stage glaucoma, one should discuss extensively with the patient the benefits and the risks from such a procedure. At the same time, the risk of blindness as a result of not having an intervention should be clearly explained to the patient.

Summary for the Clinician

- Assessing glaucoma progression is particularly difficult in end-stage glaucoma.
- The patient' s perception of deterioration may be critical in the decision for surgical intervention in end-stage glaucoma.
- Evidence suggests that trabeculectomy and aqueous shunts are comparable in terms of IOP control and duration of benefit. However, the outcomes of aqueous shunts have not been assessed in patient with end-stage glaucoma.

42.2 What Is the Patient's Risk of Losing Vision from a Glaucoma Procedure?

42.2.1 What Complications Can Occur from Glaucoma Surgery in End-Stage Glaucoma?

Despite the advantages of glaucoma surgery compared to medical treatment in terms of lowering [12] and potentially stabilizing IOP [25, 26], visually devastating complications are possible and include: chronic hypotony (leading to hypotony maculopathy), retinal detachment, aqueous misdirection, corneal complications (corneal decompensation or corneal graft failure), endophthalmitis, and phthisis bulbi [63–65]. All of the complications above are generally characterized as early complications, except for endophthalmitis and phthisis bulbi, which are considered to be late-onset complications [63]. Other complications, such as shallow anterior chamber, hyphema, wound leak, and cataract formation, may also occur after glaucoma surgery [51, 63–71]; however, they are not directly related to irreversible visual loss and therefore are not described in this section.

42.2.2 What Is the Risk of Visually Devastating Complications After Trabeculectomy?

Reported complication rates vary significantly among studies. Hypotony maculopathy has been reported to occur in 2.1–20 % of patients undergoing trabeculectomy with MMC [39, 72–82]. However, all hypotonous eyes do not develop maculopathy and IOP alone does not determine which eyes will develop macular folds [38, 41, 42, 83]. Retinal detachment is either very rare ≤0.2 % [73] or not mentioned among the postoperative complications of trabeculectomy [39, 51, 63, 66, 69, 83–87]. Based on the Medicare database of 27,886 cases of trabeculectomy, the incidence of late-onset endophthalmitis was 0.15 % per year. With a 12.8 year average duration of glaucoma in white patients, this translates to an approximately 2 % risk of visual loss from this complication [88]. It is well known that visual outcomes following endophthalmitis are generally poor, despite aggressive treatment of the infection [89, 90]. This major complication has been associated with both bleb leakage [89–92] and the use of antifibrotic agents [91–93]. The latter is in accordance with histologic studies suggesting that the use of antifibrotic agents is related to avascular blebs, characterized by thinner epithelium and more atrophic stroma [94, 95]. Aqueous misdirection, phthisis bulbi and corneal complications have a low incidence after filtering surgery. Based on the National Survey of Trabeculectomy in Britain, of the 1240 cases of open-angle glaucoma undergoing trabeculectomy, 0.2 % presented with aqueous misdirection while no cases of phthisis bulbi were reported [63]. In the same study, only 1 case (0.1 %) of band keratopathy occurred.

42.2.3 What Is the Risk of Vision Loss Following Trabeculectomy in End-Stage Glaucoma?

Only two prospective studies have evaluated the effect of filtration surgery on visual acuity and

VF in patients with advanced glaucoma. In the study by Topouzis et al. (21 eyes with an AGIS score >16), transient hypotony occurred in 3 eyes (14.2 %), while one eye presented with more extended hypotony, which resolved by the 3-month visit [42]. There were no cases with vision loss. In the study by Fujishiro et al. (27 eyes with mean deviation in the VF ≤−20 dB), after 12 months there was little change in the central 10° VF and only 1 eye (4 %) had a clinically significant decrease in visual acuity without apparent cause [44]. Also, in a comprehensive retrospective study involving a large proportion of patients with advanced glaucoma undergoing trabeculectomy with MMC, Law et al. report that vision loss occurred in 7 out of 117 patients (6 %); among them three cases presented with hypotony maculopathy (2.5 %), two cases with uncontrolled elevated intraocular pressures (1.7 %), one case with progressive cataract (0.8 %), and one case with inflammatory reaction (0.8 %) [41]. In all these cases, there was an identifiable cause for vision loss.

42.2.4 What Is the Risk of Visually Devastating Complications After an Aqueous Shunt?

In an RCT Wilson et al. compared the long-term results of trabeculectomy and Ahmed Glaucoma Valve (AGV) implantation in previously unoperated eyes with primary glaucoma. Visual acuity, VF and postoperative complications appeared to be comparable between the two groups for at least 3 to 4 years [67]. In the TVT study after 5 years of follow-up, the incidence of serious complications was 20–22 %, similarly between the tube and the trabeculectomy group, with persistent corneal edema being the most common cause for loss of two or more lines of Snellen visual acuity [49]. However, it has been pointed out that the rate of complications of trabeculectomy in the TVT study is significantly higher as compared to anecdotal results and previously published data [50, 51]. In addition, not all aqueous shunts are the same. In two large RCTs comparing the Ahmed valve with the Baerveldt tube (Ahmed Versus Baerveldt (AVB) Study [96] and Ahmed Baerveldt Comparison (ABC) Study) [97], the Baerveldt group experienced more serious postoperative complications than the Ahmed group. However, none of the above studies exclusively included patients with end-stage glaucoma.

42.2.5 What Is the Risk of Visually Devastating Complications After Cycloablation?

Cyclocryotherapy has been associated with high risk of phthisis bulbi, loss of vision, intraocular bleeding, and prolonged hypotony [98, 99]. However, studies evaluating the safety of TCP report much lower rates of major complications [56]. In primary open-angle glaucoma and pseudoexfoliation glaucoma the reported complication rates for hypotony and phthisis are 0–1.1 % and 0–1.6 %, respectively [57, 58, 100]. However, according to a recent review, loss of two or more lines of visual acuity is a common complication of TCP, with a frequency of 22.5 % on average [56]. Low rates of visually devastating complications have also been reported for ECP, although choroidal hemorrhage and endophthalmitis are potential severe complications, owing to the intraocular nature of ECP [56].

42.2.6 What Is the Risk of "Wipe-Out" Phenomenon?

There are reports of sudden loss of visual acuity in the immediate postoperative period in end-stage glaucoma with no apparent ocular pathology to account for this decline, the so-called wipe-out phenomenon [101–104]. Reports from the literature are controversial with some identifying the risk of wipe-out phenomenon as high as 14 % [102], while others regard this phenomenon as extremely rare [105]. However, because most of these studies were retrospective with inherent limitations in their ability to identify causes of vision loss, they fail to provide conclusive data on the risk of the wipe-out phenomenon in patients with advanced visual field

loss undergoing glaucoma procedures [101–107]. More recent prospective studies offer the opportunity to revisit this issue. In the study by Topouzis et al, 3 months after trabeculectomy IOP was reduced effectively and vision was preserved with no occurrences of wipe-out phenomenon [42]. In the study by Fujishiro et al, although 1 out of 27 eyes (4 %) had a clinically significant decrease in visual acuity without apparent cause, no case showed deterioration of visual acuity to 20/200 or loss of central VF [44]. Similarly, in the retrospective study by Law et al. surgical complications were the only statistically significant factor associated with severe loss of central vision and the wipe-out phenomenon was not observed [41]. In other retrospective studies assessing the outcomes of trabeculectomy specifically in advanced glaucoma no patients experienced wipe-out phenomenon [43, 45, 46]. Although no cases of wipe-out phenomenon occurred in the studies above, there is not enough evidence from the literature to exclude this possibility in very rare instances.

Summary for the Clinician

- The risk of visually devastating complications from glaucoma surgery in end-stage glaucoma is generally low.
- Complication rates of glaucoma surgery do not seem to be different in end-stage glaucoma compared to earlier stages.
- Early studies have described the wipe-out phenomenon as a postoperative immediate unexplained visual loss. Newer studies suggest that it is, at most, a rare phenomenon.

42.3 How May One Decrease the Risk of Complications from Glaucoma Surgery?

Despite the risk of vision loss from surgical complications, when the latter are factored into the risk/benefit equation, surgical options should be strongly considered in end-stage glaucoma patients [42, 108]. Further, the refinement of glaucoma surgery techniques and measures of perioperative care may favor the prognosis of an end-stage glaucoma patient undergoing surgery [43, 108]. In a recent retrospective cohort study of 292 glaucoma patients undergoing trabeculectomy with MMC, both hypotony maculopathy and endophthalmitis were found at much lower rates than previously reported [83]. According to the authors, this could be attributed to the low dose, short duration, and large area of application of MMC, along with the use of tight scleral flap sutures to avoid early overfiltration and the management of possible underfiltration with laser suture lysis.

Scleral flap closure with tightly tied sutures [43, 51, 83, 108] and intraoperative evaluation and adjustment of flow are strongly recommended. Also, based on clinical experience the use of tight conjunctival sutures seems to enhance a favorable surgical result. Postoperatively, careful IOP measurement is indicated to detect early IOP spikes, which could result in further damage of an already compromised optic nerve. Step-by-step IOP reduction with postoperative removal of releasable sutures or laser suture lysis is important to avoid hypotony [41, 43, 108]. During follow-up visits bleb leakage and signs of inflammation should always be assessed.

Summary for the Clinician

- Tight scleral flap sutures to avoid early hypotony and step-by-step IOP reduction in the postoperative period can minimize the risk of surgical complications.
- Bleb leaks and inflammation should be carefully followed and treated.

References

1. Gillies WE, Brooks AM, Strang NT. Management and prognosis of end stage glaucoma. Clin Experiment Ophthalmol. 2000;28(6):405–8.
2. The Advanced Glaucoma Intervention Study Investigators. Advanced Glaucoma Intervention

Study: 2. Visual field test scoring and reliability. Ophthalmology. 1994;101(8):1445–55.
3. Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol. 2006;141(1):24–30.
4. Iester M, Zingirian M. Quality of life in patients with early, moderate and advanced glaucoma. Eye (Lond). 2002;16(1):44–9.
5. Hattenhauer MG, Johnson DH, Ing HH, et al. The probability of blindness from open-angle glaucoma. Ophthalmology. 1998;105(11):2099–104.
6. Mikelberg FS, Schulzer M, Drance SM, et al. The rate of progression of scotomas in glaucoma. Am J Ophthalmol. 1986;101(1):1–6.
7. Wilson R, Walker AM, Dueker DK, et al. Risk factors for rate of progression of glaucomatous visual field loss: a computer-based analysis. Arch Ophthalmol. 1982;100(5):737–41.
8. Gessesse GW, Damji KF. Advanced glaucoma: management pearls. Middle East Afr J Ophthalmol. 2013;20(2):131–41.
9. Zalta AH. Use of a central 10 degrees field and size V stimulus to evaluate and monitor small central islands of vision in end stage glaucoma. Br J Ophthalmol. 1991;75(3):151–4.
10. Kim J, Dally LG, Ederer F, et al. The Advanced Glaucoma Intervention Study (AGIS): 14. Distinguishing progression of glaucoma from visual field fluctuations. Ophthalmology. 2004; 111(11):2109–16.
11. Bartz-Schmidt KU, Thumann G, Jonescu-Cuypers CP, et al. Quantitative morphologic and functional evaluation of the optic nerve head in chronic open-angle glaucoma. Surv Ophthalmol. 1999;44 Suppl 1:S41–53.
12. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in The Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology. 2001;108(11):1943–53.
13. Heijl A, Leske MC, Bengtsson B, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268–79.
14. Nouri-Mahdavi K, Hoffman D, Coleman AL, et al. Advanced Glaucoma Intervention Study. Predictive factors for glaucomatous visual field progression in the Advanced Glaucoma Intervention Study. Ophthalmology. 2004;111(9):1627–35.
15. Singh K, Lee BL, Wilson MR, Glaucoma Modified RAND-Like Methodology Group. A panel assessment of glaucoma management: modification of existing RAND-like methodology for consensus in ophthalmology. Part II: results and interpretation. Am J Ophthalmol. 2008;145(3):575–81.
16. Viswanathan AC, McNaught AI, Poinoosawmy D, et al. Severity and stability of glaucoma: patient perception compared with objective measurement. Arch Ophthalmol. 1999;117(4):450–4.
17. Malerbi FK, Hatanaka M, Vessani RM, et al. Intraocular pressure variability in patients who reached target intraocular pressure. Br J Ophthalmol. 2005;89(5):540–2.
18. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. The AGIS Investigators. Am J Ophthalmol. 2000;130(4): 429–40.
19. Collaer N, Zeyen T, Caprioli J. Sequential office pressure measurements in the management of glaucoma. J Glaucoma. 2005;14(3):196–200.
20. Bergea B, Bodin L, Svedbergh B. Impact of intraocular pressure regulation on visual fields in open-angle glaucoma. Ophthalmology. 1999;106(5):997–1004, discussion 1004–5.
21. O'Brien C, Schwartz B, Takamoto T, et al. Intraocular pressure and the rate of visual field loss in chronic open-angle glaucoma. Am J Ophthalmol. 1991;111(4):491–500.
22. Stewart WC, Kolker AE, Sharpe ED, et al. Factors associated with long-term progression or stability in primary open-angle glaucoma. Am J Ophthalmol. 2000;130(3):274–9.
23. Caprioli J, Coleman AL. Intraocular pressure fluctuation a risk factor for visual field progression at low intraocular pressures in the advanced glaucoma intervention study. Ophthalmology. 2008;115(7):1123–9.
24. Bengtsson B, Leske MC, Hyman L, et al. Fluctuation of intraocular pressure and glaucoma progression in the Early Manifest Glaucoma Trial. Ophthalmology. 2007;114(2):205–9.
25. Konstas A, Topouzis F, Leliopoulou O et al. 24-Hour intraocular pressure control with maximum medical therapy compared with surgery in patients with advanced open-angle glaucoma. Ophthalmology. 2006;113(5):761–5.e1.
26. Medeiros FA, Pinheiro A, Moura FC, et al. Intraocular pressure fluctuations in medical versus surgically treated glaucomatous patients. J Ocul Pharmacol Ther. 2002;18(6):489–98.
27. Ng WS, Agarwal PK, Sidiki S, et al. The effect of socio-economic deprivation on severity of glaucoma at presentation. Br J Ophthalmol. 2010;94(1):85–7.
28. Buys YM, Gaspo R, Kwok K, Canadian Glaucoma Risk Factor Study Group. Referral source, symptoms, and severity at diagnosis of ocular hypertension or open-angle glaucoma in various practices. Can J Ophthalmol. 2012;47(3):217–22.
29. Glaucoma; diagnosis and management of chronic open angle glaucoma and ocular hypertension CG85. London: National Institute for Health and Clinical Excellence (NICE); 2009.
30. Burr J, Azuara-Blanco A, Avenell A. Medical versus surgical interventions for open angle glaucoma. Cochrane Database Syst Rev. 2005;(2):CD004399.
31. Cairns JE. Trabeculectomy: preliminary report of a new method. Am J Ophthalmol. 1968;66(4): 673–9.

32. Watson PG. Trabeculectomy. A modified Ab. Externo technique. Ann Ophthalmol. 1970;2:199–206.
33. de Barros DS, Gheith ME, Siam GA, et al. Releasable suture technique. J Glaucoma. 2008;17(5):414–21.
34. Cohen JS, Osher RH. Releasable scleral flap suture. Ophthalmol Clin North Am. 1988;1:187–97.
35. Savage JA, Condon GP, Lytle RA, et al. Laser suture lysis after trabeculectomy. Ophthalmology. 1988;95(12):1631–8.
36. Wilkins M, Indar A, Wormald R. Intra-operative mitomycin C for glaucoma surgery. Cochrane Database Syst Rev. 2001;(1):CD002897.
37. Dhingra S, Khaw PT. The moorfields safer surgery system. Middle East Afr J Ophthalmol. 2009;16(3): 112–5.
38. Jampel HD, Solus JF, Tracey PA, et al. Outcomes and bleb-related complications of trabeculectomy. Ophthalmology. 2012;119(4):712–22.
39. Kirwan JF, Lockwood AJ, Shah P, et al. Trabeculectomy in the 21st century: a multicenter analysis. Ophthalmology. 2013;120(12):2532–9.
40. Shah P, Agrawal P, Khaw PT, et al. ReGAE 7: long-term outcomes of augmented trabeculectomy with mitomycin C in African Caribbean patients. Clin Experiment Ophthalmol. 2012;40(4):e176–82.
41. Law SK, Nguyen AM, Coleman AL, et al. Severe loss of central vision in patients with advanced glaucoma undergoing trabeculectomy. Arch Ophthalmol. 2007;125(8):1044–50.
42. Topouzis F, Tranos P, Koskosas A, et al. Risk of sudden visual loss following filtration surgery in end-stage glaucoma. Am J Ophthalmol. 2005;140(4):661–6.
43. Awai M, Koga T, Inatani M, et al. Stability of the central visual field after modern trabeculectomy techniques in eyes with advanced glaucoma. Jpn J Ophthalmol. 2007;51(2):116–20.
44. Fujishiro T, Mayama C, Aihara M, Tomidokoro A, Araie M, et al. Central 10-degree visual field change following trabeculectomy in advanced open-angle glaucoma. Eye (Lond). 2011;25(7):866–71.
45. Stead RE, King AJ. Outcome of trabeculectomy with mitomycin C in patients with advanced glaucoma. Br J Ophthalmol. 2011;95(7):960–5.
46. Baser EF, Seymenoglu G, Mayali H. Trabeculectomy for advanced glaucoma. Int Ophthalmol. 2011;31(6):439–46.
47. American National Standard for Ophthalmics: aqueous shunts for glaucoma application. ANSI Z80.27–2001. Merrifield: Optical Laboratories Association; 2001. p. 2.
48. Minckler DS, Francis BA, Hodapp EA, et al. Aqueous shunts in glaucoma: a report by the American Academy of Ophthalmology. Ophthalmology. 2008; 115(6):1089–98.
49. Gedde SJ, Schiffman JC, Feuer WJ, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. Am J Ophthalmol. 2012;153(5):789–803.
50. Caprioli J. The tube versus trabeculectomy study: why its findings may not change clinical practice? Am J Ophthalmol. 2011;151(5):742–4.
51. Jampel HD, Musch DC, Gillespie BW, et al. Perioperative complications of trabeculectomy in the collaborative initial glaucoma treatment study (CIGTS). Am J Ophthalmol. 2005;140(1):16–22.
52. Rulli E, Biagioli E, Riva I, et al. Efficacy and safety of trabeculectomy vs nonpenetrating surgical procedures: a systematic review and meta-analysis. JAMA Ophthalmol. 2013;131(12):1573–82.
53. Francis BA, Singh K, Lin SC, et al. Novel glaucoma procedures: a report by the American Academy of Ophthalmology. Ophthalmology. 2011;118(7):1466–80.
54. Goldenberg-Cohen N, Bahar I, Ostashinski M, et al. Cyclocryotherapy versus transscleral diode laser cyclophotocoagulation for uncontrolled intraocular pressure. Ophthalmic Surg Lasers Imaging. 2005; 36(4):272–9.
55. Schlote T, Derse M, Rassmann K, et al. Efficacy and safety of contact transscleral diode laser cyclophotocoagulation for advanced glaucoma. J Glaucoma. 2001;10(4):294–301.
56. Ishida K. Update on results and complications of cyclophotocoagulation. Curr Opin Ophthalmol. 2013;24(2):102–10.
57. Egbert PR, Fiadoyor S, Budenz DL, et al. Diode laser transscleral cyclophotocoagulation as a primary surgical treatment for primary open-angle glaucoma. Arch Ophthalmol. 2001;119(3):345–50.
58. Grueb M, Rohrbach JM, Bartz-Schmidt KU, et al. Transscleral diode laser cyclophotocoagulation as primary and secondary surgical treatment in primary open-angle and pseudoexfoliatve glaucoma. Long-term clinical outcomes. Graefes Arch Clin Exp Ophthalmol. 2006;244(10):1293–9.
59. Lai JS, Tham CC, Chan JC, et al. Diode laser transscleral cyclophotocoagulation as primary surgical treatment for medically uncontrolled chronic angle closure glaucoma: long-term clinical outcomes. J Glaucoma. 2005;14(2):114–9.
60. Kaplowitz K, Kuei A, Klenofsky B et al. The use of endoscopic cyclophotocoagulation for moderate to advanced glaucoma. Acta Ophthalmol. 2015;93:395–401. Epub ahead of print.
61. Souza C, Tran DH, Loman J, et al. Long-term outcomes of Ahmed glaucoma valve implantation in refractory glaucomas. Am J Ophthalmol. 2007; 144(6):893–900.
62. Baudouin C, Liang H, Hamard P, et al. The ocular surface of glaucoma patients treated over the long term expresses inflammatory markers related to both T-helper 1 and T-helper 2 pathways. Ophthalmology. 2008;115(1):109–15.
63. Edmunds B, Thompson JR, Salmon JF, et al. The National Survey of Trabeculectomy. III. Early and late complications. Eye (Lond). 2002;16(3):297–303.

64. Coleman AL, Hill R, Wilson MR, et al. Initial clinical experience with the Ahmed Glaucoma Valve implant. Am J Ophthalmol. 1995;120(1):23–31.
65. Topouzis F, Coleman AL, Choplin N, et al. Follow-up of the original cohort with the Ahmed glaucoma valve implant. Am J Ophthalmol. 1999;128(2):198–204.
66. Wilson MR, Mendis U, Smith SD, et al. Ahmed glaucoma valve implant vs trabeculectomy in the surgical treatment of glaucoma: a randomized clinical trial. Am J Ophthalmol. 2000;130(3):267–73.
67. Wilson MR, Mendis U, Paliwal A, et al. Long-term follow-up of primary glaucoma surgery with Ahmed glaucoma valve implant versus trabeculectomy. Am J Ophthalmol. 2003;136(3):464–70.
68. Lamping KA, Bellows AR, Hutchinson BT, et al. Long-term evaluation of initial filtration surgery. Ophthalmology. 1986;93(1):91–101.
69. Parc CE, Johnson DH, Oliver JE, et al. The long-term outcome of glaucoma filtration surgery. Am J Ophthalmol. 2001;132(1):27–35.
70. Ehrnrooth P, Puska P, Lehto I, et al. Progression of visual field defects and visual loss in trabeculectomized eyes. Graefes Arch Clin Exp Ophthalmol. 2005; 243(8):741–7.
71. AGIS (Advanced Glaucoma Intervention Study) Investigators. The Advanced Glaucoma Intervention Study 8: risk of cataract formation after trabeculectomy. Arch Ophthalmol. 2001;119(12):1771–9.
72. Bindlish R, Condon G, Schlosser J, et al. Efficacy and safety of mitomycin-C in primary trabeculectomy. Five-year follow-up. Ophthalmology. 2002;109(7):1336–41, discussion 1341–2.
73. Costa VP, Moster MR, Wilson RP, et al. Effects of topical mitomycin C on primary trabeculectomies and combined procedures. Br J Ophthalmol. 1993; 77(11):693–7.
74. Shields MB, Scroggs MW, Sloop CM, et al. Clinical and histopathologic observations concerning hypotony after trabeculectomy with adjunctive mitomycin C. Am J Ophthalmol. 1993;116(6):673–83.
75. Kitazawa Y, Suemori-Matsushita H, Yamamoto T, et al. Low-dose and high-dose mitomycin trabeculectomy as an initial surgery in primary open-angle glaucoma. Ophthalmology. 1993;100(11):1624–8.
76. Mégevand GS, Salmon JF, Scholtz RP, et al. The effect of reducing the exposure time of mitomycin C in glaucoma filtering surgery. Ophthalmology. 1995;102(1):84–90.
77. Cheung JC, Wright MM, Murali S, et al. Intermediate-term outcome of variable dose mitomycin C filtering surgery. Ophthalmology. 1997;104(1):143–9.
78. Perkins TW, Gangnon R, Ladd W, et al. Trabeculectomy with mitomycin C: intermediate-term results. J Glaucoma. 1998;7(4):230–6.
79. Rasheed e-S. Initial trabeculectomy with intraoperative mitomycin-C application in primary glaucomas. Ophthalmic Surg Lasers. 1999;30(5):360–6.
80. Mietz H, Krieglstein GK. Suramin to enhance glaucoma filtering procedures: a clinical comparison with mitomycin. Ophthalmic Surg Lasers. 2001; 32(5):358–69.
81. Mietz H, Jacobi PC, Krieglstein GK. Intraoperative episcleral versus postoperative topical application of mitomycin-C for trabeculectomies. Ophthalmology. 2002;109(7):1343–9.
82. Tsai JC, Chang HW, Kao CN, et al. Trabeculectomy with mitomycin C versus trabeculectomy alone for juvenile primary open-angle glaucoma. Ophthalmologica. 2003;217(1):24–30.
83. Fontana H, Nouri-Mahdavi K, Lumba J, et al. Trabeculectomy with mitomycin C: outcomes and risk factors for failure in phakic open-angle glaucoma. Ophthalmology. 2006;113(6):930–6.
84. Shigeeda T, Tomidokoro A, Chen YN, et al. Long-term follow-up of initial trabeculectomy with mitomycin C for primary open-angle glaucoma in Japanese patients. J Glaucoma. 2006;15(3):195–9.
85. Lüke C, Dietlein TS, Jacobi PC, et al. A prospective randomized trial of viscocanalostomy versus trabeculectomy in open-angle glaucoma: a 1-year follow-up study. J Glaucoma. 2002;11(4):294–9.
86. Ehrnrooth P, Lehto I, Puska P, et al. Effects of early postoperative complications and the location of trephined block on long-term intraocular pressure control after trabeculectomy. Graefes Arch Clin Exp Ophthalmol. 2003;241(10):803–8.
87. Landers J, Martin K, Sarkies N, et al. A twenty-year follow-up study of trabeculectomy: risk factors and outcomes. Ophthalmology. 2012;119(4):694–702.
88. Quigley HA. Reappraising the risk and benefits of aggressive glaucoma therapy. Ophthalmology. 1997;104(12):1985–6.
89. Song A, Scott IU, Flynn Jr HW, et al. Delayed-onset bleb-associated endophthalmitis: clinical features and visual acuity outcomes. Ophthalmology. 2002; 109(5):985–91.
90. Soltau JB, Rothman RF, Budenz DL, et al. Risk factors for glaucoma filtering bleb infections. Arch Ophthalmol. 2000;118(3):338–42.
91. Higginbotham EJ, Stevens RK, Musch DC, et al. Bleb-related endophthalmitis after trabeculectomy with mitomycin C. Ophthalmology. 1996;103(4): 650–6.
92. Susanna Jr R, Takahashi W, Nicolela M. Late bleb leakage after trabeculectomy with 5-fluorouracil or mitomycin C. Can J Ophthalmol. 1996;31(6): 296–300.
93. Greenfield DS, Suner IJ, Miller MP, et al. Endophthalmitis after filtering surgery with mitomycin. Arch Ophthalmol. 1996;114(8):943–9.
94. Mietz H, Arnold G, Kirchhof B, et al. Histopathology of episcleral fibrosis after trabeculectomy with and without mitomycin C. Graefes Arch Clin Exp Ophthalmol. 1996;234(6):364–8.

95. Mietz H, Brunner R, Addicks K, et al. Histopathology of an avascular filtering bleb after trabeculectomy with mitomycin C. J Glaucoma. 1993;2(4):266–70.
96. Christakis PG, Tsai JC, Kalenak JW, et al. The Ahmed versus Baerveldt study: three-year treatment outcomes. Ophthalmology. 2013;120(11):2232–40.
97. Budenz DL, Barton K, Feuer WJ, et al. Treatment outcomes in the Ahmed Baerveldt Comparison Study after 1 year of follow-up. Ophthalmology. 2011;118(3):443–52.
98. Caprioli J, Strang SL, Spaeth GL, et al. Cyclocryotherapy in the treatment of advanced glaucoma. Ophthalmology. 1985;92(7):947–54.
99. Benson MT, Nelson ME. Cyclocryotherapy: a review of cases over a 10-year period. Br J Ophthalmol. 1990;74(2):103–5.
100. Kramp K, Vick HP, Guthoff R. Transscleral diode laser contact cyclophotocoagulation in the treatment of different glaucomas, also as primary surgery. Graefes Arch Clin Exp Ophthalmol. 2002;240(9):698–703.
101. Aggarwal SP, Hendeles S. Risk of sudden visual loss following trabeculectomy in advanced primary open-angle glaucoma. Br J Ophthalmol. 1986;70(2):97–9.
102. Kolker AE. Visual prognosis in advanced glaucoma: a comparison of medical and surgical therapy for retention of vision in 101 eyes with advanced glaucoma. Trans Am Ophthalmol Soc. 1977;75:539–55.
103. Otto J. Loss of point of fixation after glaucoma surgery. Klin Monbl Augenheilkd Augenarztl Fortbild. 1957;131(2):178–95.
104. Costa VP, Smith M, Spaeth GL, et al. Loss of visual acuity after trabeculectomy. Ophthalmology. 1993;100(5):599–612.
105. Lichter PR, Ravin JG. Risks of sudden visual loss after glaucoma surgery. Am J Ophthalmol. 1974;78(6):1009–13.
106. O'Connell EJ, Karseras AG. Intraocular surgery in advanced glaucoma. Br J Ophthalmol. 1976;60(2):124–31.
107. Martinez JA, Brown RH, Lynch MG, et al. Risk of postoperative visual loss in advanced glaucoma. Am J Ophthalmol. 1993;115(3):332–7.
108. Moster MR, Moster ML. Wipe-out: a complication of glaucoma surgery or just a blast from the past? Am J Ophthalmol. 2005;140(4):705–6.

Glaucomas: Managing Normal-Tension Glaucoma

43

Kazuhisa Sugiyama and Yoshiaki Kitazawa

Core Messages

- There is no single clearly defined intraocular pressure (IOP) level below which an eye with normal-tension glaucoma (NTG) is safe from further damage.
- Susceptibility to IOP-mediated damage varies from patient to patient.
- It can be particularly difficult to distinguish a true pharmacological effect on IOP from IOP fluctuation in NTG.
- IOP lowering in NTG can be achieved with medication, laser, or surgery.
- NTG patients with a history of recurring disc hemorrhages, migraine, female gender, and advanced field loss may progress more rapidly than other NTG patients and should be monitored more closely.

43.1 How Low an Intraocular Pressure Do I Need to Target in Normal-Tension Glaucoma?

Information available in the literature on how to determine the target pressure for a normal-tension glaucoma (NTG) patient is scarce. In the Collaborative Normal-Tension Glaucoma Study (CNTGS) [1, 2], there is no clearly defined single intraocular pressure (IOP) level below which an individual eye is completely safe from developing further glaucomatous damage. In the CNTGS, progression occurred in 35 % of untreated eyes (mean IOP 16.0 mmHg) vs. 12 % of treated eyes (mean IOP 10.6 mmHg reduced from a mean baseline IOP of 16.9 mmHg). Probability of nonprogression (or survival) in NTG patients determined by the Kaplan–Meier life table analysis is shown in Fig. 43.1 [2]. Importantly, the study also demonstrated that many patients with NTG in the untreated randomization arm did not progress. Additionally, a number of enrolled patients showed no progression while in the prerandomization observation phase and were therefore never randomly assigned to either the treatment or nontreatment arms. (The CNTGS enrolled 230 patients but did not randomize them to either arm of the study [observation arm vs. a 30 % IOP reduction arm] unless they showed a visual field defect threatening fixation or had had recent glaucomatous progression in the visual field or on the optic nerve.) It was

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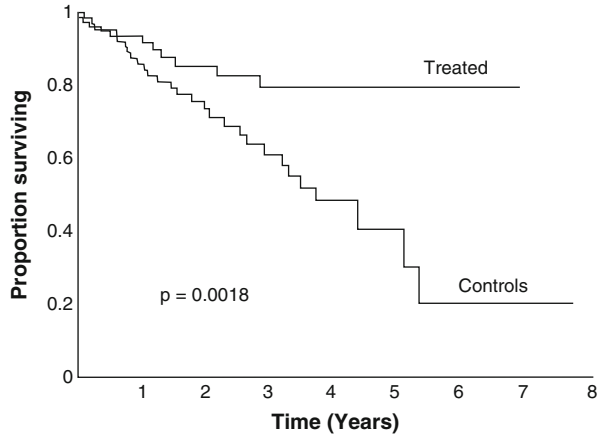

Fig. 43.1 From CNTGS, survival curves of end points (optic nerve or visual field progression) in untreated controls and treated subjects (30 % IOP reduction). Visual field baselines were obtained at randomization using four of five defined end points. Data of eyes that developed cataracts were censored at the time of cataract diagnosis. With this adjustment, the survival experience became significantly better for the treated group than the control subjects ($p=0.0018$). The survival analysis showed a survival of 80 % in the treated arm, 60 % in the control arm at 3 years, and 80 % in the treated arm and 40 % in the controls at 5 years [2]

concluded that those patients destined to be nonprogressors or only to progress slowly would derive little benefit, if any, from treatment. Moreover, it should be noted that although progression was less likely in the treated arm a number of patients' glaucoma continued to progress despite the 30 % IOP reduction from baseline.

This points to the fact that individuals vary in their susceptibility to IOP-dependent damage, and there is no universally safe IOP value that can be guaranteed to prevent further glaucomatous damage in everyone. An optic nerve that has already been damaged appears to be more susceptible to further pressure-mediated injury, so patients with advanced glaucomatous neuropathy may require very low target pressures to halt the disease, although the exact level of IOP is unknown.

The target pressure should not be thought of as a single value; rather, it should be thought of as a range of acceptable IOPs. In determining an appropriate target pressure range for an individual patient, the ophthalmologist must take into account several factors: (1) the IOP level at which optic nerve damage previously occurred; (2) the extent and rate of progression of glaucomatous damage, if known; (3) the presence of other risk factors for glaucoma; and (4) the patient's age, expected life span, and medical history. Of these four major factors, the first three help determine the target IOP range, whereas the last one determines how aggressive one should be in maintaining the patient in that range. Although a clinician may not always know when optic nerve damage first occurred, the rate of progression can be measured on routine follow-up, provided that accurate baselines of disc structure and visual field sensitivities have been established. In addition, it is advisable to evaluate risk factors, such as disc hemorrhage, migraine, female gender, diabetes, cardiovascular disease, sleep apnea, and vasospastic syndromes, as patients with multiple risk factors may progress more rapidly [3]. Genetic risk in terms of family history of glaucoma should also be taken into account.

A target IOP that is appropriate when you first see a patient may not be a safe pressure 10 years later after progressive nerve or field damage has occurred. The clinician must reevaluate each glaucoma patient at regular intervals specifically looking for signs of possible progression of optic disc and visual field loss that have occurred in the initially set target IOP range.

Summary for the Clinician

- There is no universally safe IOP level for NTG patients.
- There is little specific guidance on how to select a target IOP in NTG; however, an optic nerve that has already sustained damage appears to be more susceptible to pressure-mediated injury, so patients with advanced glaucomatous neuropathy may require very low target pressures to halt the disease.
- In the CNTGS, a 30 % IOP target reduction from baseline was selected; despite this significant reduction, some patients' glaucoma progressed.
- The CNTGS also demonstrated that many NTG patients on no treatment did not progress over the 5-year study period.
- Individuals may vary in their susceptibility to IOP-dependent damage.
- Target IOP should be a range that is readjusted based on progression, risk factors, and expected life span.

43.2 If a Patient with Normal-Tension Glaucoma Is Started on Topical Medication and the Intraocular Pressure Is Lowered 1–2 mmHg, Can I Consider That To Be Adequate Treatment?

Whether an IOP reduction of 1–2 mmHg is adequate or not depends on the baseline IOP and the desired target pressure for the particular eye, as mentioned in the previous section. If a given NTG patient has a baseline IOP of 14 mmHg and a presumed target pressure of 12 mmHg, then 2 mmHg of IOP reduction might be regarded as adequate. On the other hand, if the same eye has a baseline IOP of 18 mmHg and a target of 12 mmHg, then 2 mmHg of IOP reduction is not sufficient.

It is not always simple to determine the true IOP reduction produced by topical glaucoma medication in daily practice. While evaluating IOP reduction obtained by treatment, several points should be kept in mind. First, IOP measurements before and after treatment should be taken with the same type of tonometer. Different tonometry methods may give different IOP readings because of the different effects of central corneal thickness and corneal biomechanics on the pressure estimates. Also, the same physician or technician should measure IOP with manual instruments such as Goldmann applanation tonometer to reduce interobserver variability. Second, IOP exhibits various kinds of fluctuation, including diurnal, short-term (day to day), or long-term (seasonal) variations. Therefore, each IOP measurement is only a snapshot of IOP variations over time. Glaucoma patients are reported to have a larger degree of IOP fluctuations than normal subjects. If the range of IOP fluctuations is very wide, it may be difficult to know the true pharmacological effects of glaucoma medications from IOP readings. For example, an NTG patient with a baseline IOP of 18 mmHg in the affected eye had a posttreatment IOP of 15 mmHg at a follow-up visit. The IOP reduction of 3 mmHg may be merely an IOP fluctuation and may not represent a therapeutic effect. In order to differentiate a true pharmacological effect from IOP fluctuation, a one-eyed trial of medication is recommended. On the basis of an assumption that fellow eyes have spontaneous IOP fluctuations of the same size and in the same direction, subtracting the IOP change in the treated eye from that of the nontreated eye should reveal true pharmacological effect of medication (Fig. 43.2). Unfortunately, glaucoma patients are reported to have a higher degree of asymmetrical spontaneous IOP fluctuations than normal subjects [4], and thus we cannot assume that a one-eyed trial will be helpful in assessing the effect of medication. Therefore, the mean IOP level and the range of IOP fluctuation derived from a number of IOP measurements at baseline for each eye and after treatment should be recorded. There is no guideline available as to how many IOP measurements and over what period of time they should be measured.

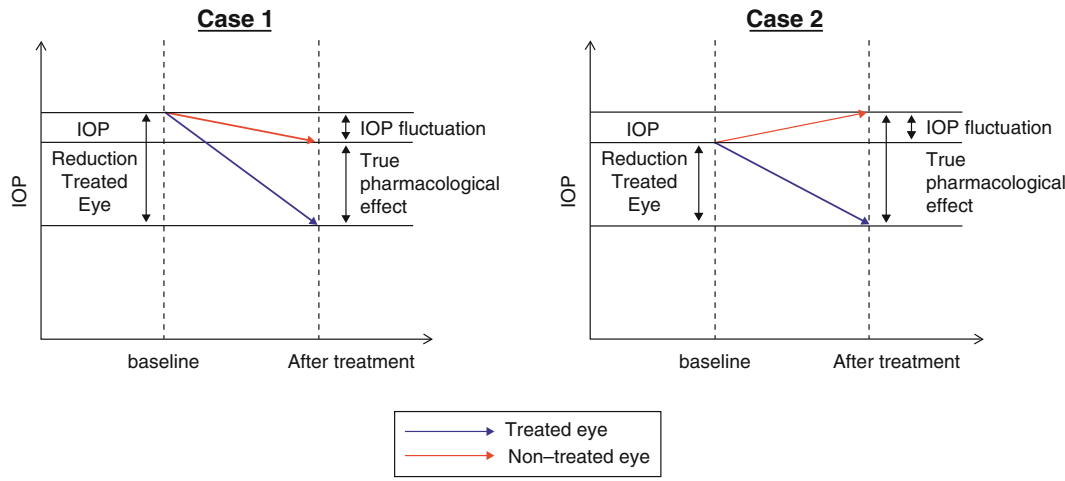

Fig. 43.2 In a one-eyed trial of topical medication, true pharmacological effect can be separated from the effect of IOP fluctuation by subtracting the IOP change of the non-treated eye (IOP fluctuation) from that of the treated eye. It may be less (case 1) or more (case 2) than the IOP reduction in the treated eye

Summary for the Clinician

- In NTG a small reduction in IOP, if consistently seen on follow-up visits, can be adequate if the target IOP is only a few points below the mean baseline IOP.
- Theoretically, a one-eyed trial of topical medication can be helpful in assessing whether a drop in IOP is due to natural fluctuation or to a medication effect.
- In reality, fellow eyes of glaucoma patients do not necessarily have parallel fluctuation of equal range, i.e., they can fluctuate independently of each other.
- One should obtain multiple IOP measurements before and after treatment for an individual eye for comparison and evaluation of whether a medication is having a true IOP-lowering effect.

43.3 What Is the Treatment of Choice in Normal-Tension Glaucoma: Medication, Laser, or Surgery?

In patients with bilateral NTG, visual field damage is usually significantly worse in the eye with higher IOP. Moreover, the risk of progression of visual-field damage increases with elevation of the mean IOP and with larger IOP fluctuation during follow-up. The CNTGS group revealed that reduction of IOP significantly decreases the probability of progressive visual field loss [1, 2]. On the basis of this information, IOP lowering by any means is good for patients with NTG.

So the next question is which treatment will maximize patients' quality of life? Surgery, especially trabeculectomy with mitomycin C, may possibly cause adverse postoperative events including hypotony maculopathy, blebitis,

endophthalmitis, leaking blebs, bleb dysesthesia, cataract, etc. These complications may threaten visual function and quality of life. In contrast, medical therapy may have short-term disadvantages such as inconvenience, cost, ocular, and systemic side effects, and noncompliance, but usually does not worsen visual function or quality of life immediately. Laser surgery is much less invasive than incisional surgery, but the IOP-lowering effect is limited. Avoiding the potential risk of an immediate decrease in quality of life with surgery is always ideal, but in some patients incisional surgery is the only way to maximize their long-term vision.

In most cases of NTG, medical therapy should be the first line of therapy. Since long-term treatment is required for glaucoma, ophthalmologists should consider a patient's quality of life and the ability to comply with treatment before choosing a particular drop. Prostaglandin analogues may be suitable for first-line therapy of NTG because of the once daily application and they have few side effects. However, the IOP-lowering effect with prostaglandin analogue can be variable and is sometimes very weak or produces no effect. In nonresponders, we consider switching to another prostaglandin analogue or to another class of medication. Additional agents must be added when the IOP reduction by monotherapy is insufficient to control visual field loss progression. When adequate IOP reduction cannot be obtained by maximal medical therapy, laser or surgical treatment is considered. However, the effects of laser therapy (argon laser trabeculoplasty and selective laser trabeculoplasty) may be limited for patients with NTG under maximal medical therapy.

Surgical options for glaucoma treatment are generally reserved as a final option, especially for NTG patients. As a surgical treatment for NTG, trabeculectomy with mitomycin C is usually performed to achieve target pressures less than 12 mmHg. Although trabeculectomy with mitomycin C may produce the desired IOP reduction, it may cause severe complications as previously mentioned.

Summary for the Clinician

- The goal of treatment for NTG is to preserve patients' visual function while maintaining quality of life.
- Medical therapy is usually the first choice for NTG treatment.
- Surgical options should be reserved as a later option, especially for NTG patients because of the greater potential for surgery to cause hypotony problems when aiming for very low pressures.
- Laser trabeculoplasty may have disappointing results in NTG, especially if patients are already on maximal medical therapy.

43.4 What Time Course of Progression Can I Expect in Normal-Tension Glaucoma Patients and Can I Predict Who May Progress Over the Short Term?

There remains a great deal to learn about the natural history of NTG and risk factors for its progression. The CNTGS showed that approximately 50 % of patients with NTG did not suffer progressive visual field loss over 5 years of observation, while about one third of patients progressed within 3 years [5] (Fig. 43.3). In general, it is reasonable to observe NTG patients closely without treatment, particularly those with early stages of visual field loss. Through regular monitoring, progression can be detected early in order to initiate treatment.

43.4.1 Risk Factors for Progression in NTG

The rate of visual field loss usually correlates with the stage of optic nerve damage. In the early stages of glaucoma, the rate of progression may be very slow but is likely to become more rapid as the

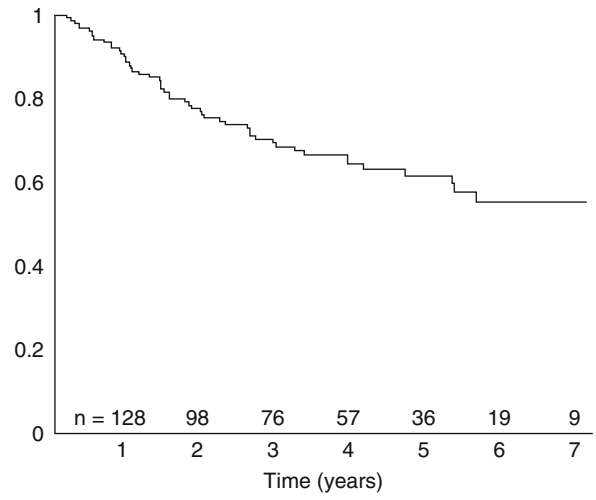

Fig. 43.3 From CNTGS, Kaplan–Meier survival curve for untreated NTG eyes (160 eyes). Estimated mean time to end point (visual field or optic nerve change) was 5.6±0.28 (SEM) years according to strictly defined criteria [5]

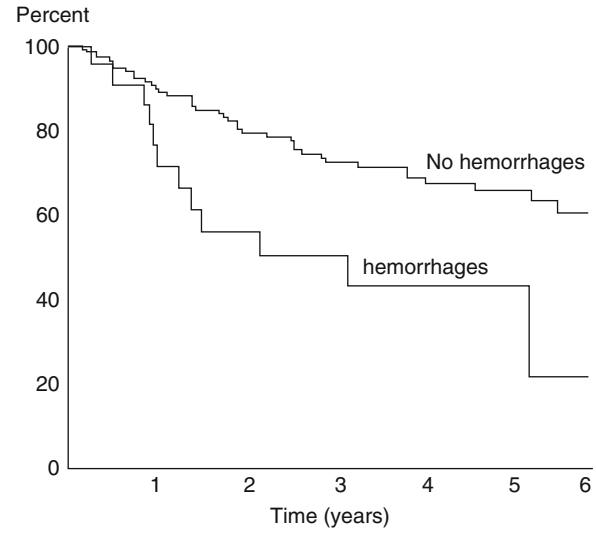

Fig. 43.4 From the CNTGS, Kaplan–Meier survival curves comparing those who did and did not have a disc hemorrhage on the initial qualifying examination with regard to first reaching a demonstrable end point [3]

glaucoma becomes more advanced. Currently, IOP is the only treatable risk factor in glaucoma. Therefore, in patients with advanced NTG IOP should be monitored more frequently. NTG patients who have known risk factors for progression, such as disc hemorrhage, migraine, and female gender are also followed more frequently by us. These factors were significantly associated with progressive visual field loss progression in the CNTGS [3] (Fig. 43.4). Above all, disc hemorrhage has been reported to be a significant negative prognostic factor in patients with NTG and may be a sign of progressive damage of the retinal nerve fiber layer.

43.4.2 Disc Hemorrhage in NTG

Recurrent disc hemorrhage is an important sign prognosticating a worse outcome. The cumulative probability of visual field deterioration was found to be significantly greater in patients with recurrent disc hemorrhage [6]. The average interval between disc hemorrhage (DH) and progression of visual field defects was 19.9±11.6 months [7]. The probability of maintaining a stable visual field was 42±17 % for patients *without* recurring disc hemorrhages and 0±0 % for patients *with* recurrent

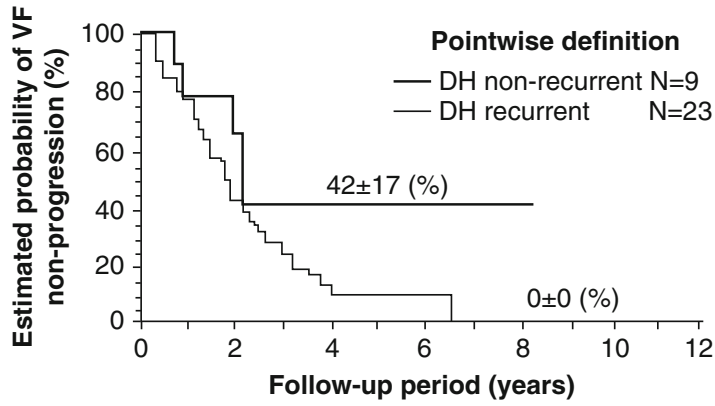

Fig. 43.5 Kaplan–Meier survival analysis plotting the probability of visual field stability—a pointwise definition of progression. *Heavier lines* show eyes with nonrecurrent disc hemorrhage and *lighter line* represents eyes with recurring disc hemorrhage. All cases with recurrent hemorrhage were associated with progression, whereas the probability of surviving was 42 % in those with nonrecurrent hemorrhage [11]

disc hemorrhages (Kaplan–Meier method) [7] (Fig. 43.5). Disc hemorrhages were four times more prevalent in NTG than in high-tension glaucoma [8]. The vast majority (80 %) of disc hemorrhages occur near the border of retinal nerve fiber layer defects and adjacent healthy looking retinal tissue [9]. The frequency of localized retinal nerve fiber layer defects was significantly greater in NTG patients with disc hemorrhages [10]. Patients with NTG and disc hemorrhages tend to show visual field progression within the central 10° of visual field [11]. Although the exact mechanism of disc hemorrhage remains unknown, it has been suggested that mechanical rupture of small blood vessels due to structural changes at the level of the lamina cribrosa accounts for at least some of these events. Disc hemorrhages may be a useful sign to identify NTG patients who are more likely to progress.

Summary for the Clinician

- Some patients with NTG will remain stable for a long period of time without IOP-lowering treatment, while others will progress rapidly.
- It is reasonable to observe NTG patients closely without treatment, particularly those with early stages of visual field loss.
- Progression occurs more rapidly in advanced stages of glaucoma and therefore these patients should be monitored more frequently for progression.
- Patients with additional risk factors for NTG may progress more quickly: disc hemorrhage, history of migraine headaches, and female gender.
- Disc hemorrhages are more prevalent in NTG than high-tension POAG.
- Recurrent disc hemorrhages have been found to be an important sign of progression.

References

1. Collaborative Normal-Tension Glaucoma Study Group. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressure. Am J Ophthalmol. 1998;126: 487–97.
2. Collaborative Normal-Tension Glaucoma Study Group. The effectiveness intraocular pressure reduction

in the treatment of normal-tension glaucoma. Am J Ophthalmol. 1998;126:498–505.
3. Drance S, Anderson DR, Schulzer M, For Collaborative Normal-tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol. 2001;131:699–708.
4. Sit AJ, Liu JH, Weinreb RN. Asymmetry of right versus left intraocular pressures over 24 hours in glaucoma patients. Ophthalmology. 2006;113:425–30.
5. Collaborative Normal-Tension Glaucoma Study Group. Natural history of normal-tension glaucoma. Ophthalmology. 2001;108:247–53.
6. Kim SH, Park KH. The relationship between recurrent optic disc hemorrhage and glaucoma progression. Ophthalmology. 2006;113:598–602.
7. Ishida K, Yamamoto T, Sugiyama K, Kitazawa Y. Disk hemorrhage is a significantly negative prognostic factor in normal-tension glaucoma. Am J Ophthalmol. 2000;129(6):707–14.
8. Kitazawa Y, Shirato S, Yamamoto T. Optic disc hemorrhage in low-tension glaucoma. Ophthalmology. 1986;93:853–7.
9. Sugiyama K, Tomita G, Kitazawa Y, et al. The association of optic disc hemorrhage with retinal nerve fiber layer defect and peripapillary atrophy in normal-tension glaucoma. Ophthalmology. 1997;104: 1926–33.
10. Sugiyama K, Uchida H, Tomita G, et al. Localized wedge-sharped defects of retinal nerve fiber layer and disc hemorrhage in glaucoma. Ophthalmology. 1999;106:1762–7.
11. Kono Y, Sugiyama K, Ishida K, et al. Characteristics of visual field progression in patients with normal-tension glaucoma with optic disk hemorrhages. Am J Ophthalmol. 2003;135:499–503.

Glaucomas: Pseudoexfoliation Glaucoma

44

Richard K. Lee

Core Messages

- The presence of pseudoexfoliation (PXF) material observed in the eye is a significant risk factor for the development of ocular hypertension and glaucoma.
- The association of PXF with systemic diseases is weak.
- Once PXF material is noted in an eye, a significant percentage of PXF eyes will develop glaucoma within 5–10 years.
- The presence of PXF material in the eye is associated with a significantly increased risk of complications during cataract surgery but cataract extraction technique can be modified to minimize complications.

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44.1 Is There a Gene for Pseudoexfoliation Syndrome?

The identity of the proteins responsible for pseudoexfoliation (PXF) glaucoma is not known [1]. However, genetic risk factors for the development of PXF material and PXF glaucoma have been identified [2]. Single nucleotide polymorphisms (SNP) in the lysyl oxidase-like 1 (LOXL1) gene are associated with PXF glaucoma in many patient populations, including Scandinavian, Japanese, Australian, and American cohorts [2–9]. LOXL1 is an enzymatic protein important in extracellular matrix metabolism and turnover. Thus, changes in the extracellular matrix have been hypothesized to be the pathophysiological mechanism responsible for the development of PXF glaucoma [1, 10].

More recently, the CACNA1A gene, which encodes a subunit of a P/Q type voltage-dependent calcium channel, has been found to be associated with a risk of developing PXF glaucoma [11]. LOXL1 and CACNA1A do not appear to intersect in molecular pathways, but calcium dysregulation may be associated with the assembly of PXF material.

Currently, genetic testing for polymorphisms for LOXL1 and CACNA1A are not indicated for PXF glaucoma susceptibility testing because the frequency of these gene polymorphisms is

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either too high in the normal population (LOXL1) or not clearly defined (CACNA1A) to be useful.

Summary for the Clinician

- Pseudoexfoliation glaucoma is associated with single nucleotide polymorphisms in LOXL1 (an extracellular matrix metabolism associated protein) and with CACNA1A (a voltage-gated calcium channel).
- Genetic testing for pseudoexfoliation glaucoma polymorphisms in LOXL1 and CACNA1A currently is not useful.

44.2 Is Pseudoexfoliation Associated with Systemic Disease?

In addition to being found in the eye, PXF material is found in tissues and organs throughout the body. Using electron microscopy and light microscopy with periodic acid Schiff staining, microfibrillar PXF material has been observed in ocular structures such as lens capsule, iris, conjunctiva, optic nerve sheath, eye muscles, and eyelids [10, 12–14]. PXF microfibrils have also been observed systemically in the lung, heart, liver, skin, and gallbladder [10, 13, 14]. It has been suggested that pseudoexfoliation is a systemic disease because PXF material is present throughout the body. Associations with vascular diseases, such as myocardial infarction, stroke, carotid disease, abdominal aortic aneurysm, and central retinal vein occlusion, are most frequently discussed [15–17]. A review of the Blue Mountains Eye Study Australian population data suggested that PXF was associated with hypertension and a history of vascular events (such as angina, heart attack, and stroke) [17]. A Croatian study reported PXF may have an association with subclinical diastolic cardiac dysfunction [18], while a Turkish study found angiographically proven coronary artery disease in PXF [19]. However, residents of Olmstead County, Minnesota with PXF did not have any increased risk of cardiovascular or cerebrovascular mortality (i.e., death from acute myocardial infarction, cerebral thrombosis, cerebral hemorrhage) [16].

The association between PXF and the extracellular matrix has led some to believe that vascular integrity may be compromised in patients with PXF. An increased incidence of abdominal aortic aneurysm has been observed [20], although this finding is controversial [21–23]. It has also been suggested that the carotid vessels are more rigid with decreased baroreflex sensitivity in PXF patients compared to age-matched controls [24, 25]. These vascular changes may be associated with elevated levels of homocysteine in the aqueous humor, tears, and plasma of PXF patients in conjunction with abnormal extracellular matrix turnover [26–29]. However, other studies have not been able to verify a biochemical or genetic association between homocysteine levels and PXF [30].

The presence of PXF material in the eye is associated with sensorineural hearing loss in age- and sex- matched controls [31, 32]. Thus, the presence of the PXF material in the ear may cause damage to hearing. The presence of PXF material in non-ocular tissues does not cause obvious changes in function or structure of these organs [10]. Although PXF is a systemic condition, its association with systemic disease is relatively weak, whereas its association with glaucoma is without doubt.

Summary for the Clinician

- Pseudoexfoliation (PXF) material is found in the eye, extra ocular tissues, and organs and tissues in the body.
- PXF has been associated with vascular disease, sensorineural hearing loss, and elevated homocysteine levels, but these associations are weak and controversial.

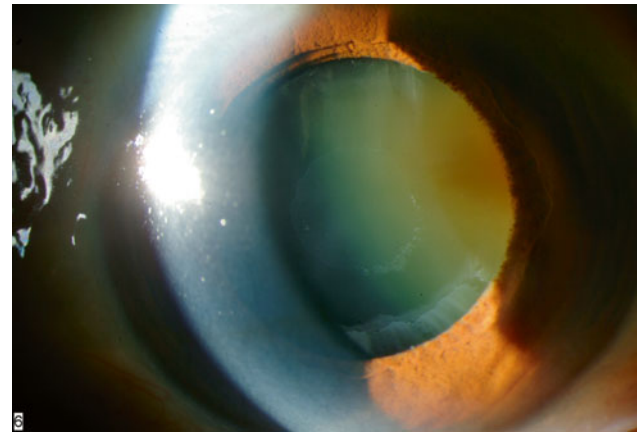

Fig. 44.1 Pseudoexfoliation (PXF) material in a bull's eye configuration on the lens capsule. Note the central and peripheral circular areas of white plaque-like PXF material on the lens capsule with a mid-peripheral clear area due to the pupil border rubbing off the capsular material

44.3 What Are Risk of Factors for Developing Pseudoexfoliation Glaucoma?

Classically, PXF material is observed in a bull's eye configuration on the anterior lens capsule (Fig. 44.1). The clinical presentation of PXF is often asymmetric both with regard to the presence of the PXF material in the eyes and the development of glaucoma. Although PXF material may only be apparent unilaterally with slit lamp biomicroscopy, the PXF material is present histologically in both eyes [33]. In a prospective 10-year study, almost one-third of observed patients converted from unilaterally to bilaterally observed PXF material in 5 years and almost 40 % in 10 years, with a mean conversion time to bilateral PXF presence of over 5 years [34]. In a community-based study, similar results were observed with a third of patients converting to bilateral PXF in 15 years [35].

The presence of PXF material in the eye is a significant risk factor for glaucoma, especially when combined with increasing age. In the Early Manifest Glaucoma Trial, 55 % of patients with PXF developed glaucoma after a mean observation period of 8.7 years [36]. The glaucoma conversion rate was twice as high as in the controls, even after matching for IOP, age, and gender [36]. In other studies, a third of eyes with PXF material developed glaucoma within 10 years [34], while an even higher rate of 44 % required treatment for glaucoma after 15 years of follow-up [35]. The conversion rate to glaucoma can occur relatively rapidly in relation to the diagnosis of PXF—94 % of those patients who converted to PXF glaucoma converted within 5 years of the detection of PXF material in the eye [34]. Interestingly, these data suggest that in a significant number of patients a long period of time may pass before visible PXF material in the eye and PXF glaucoma develop, and some patients may not develop PXF glaucoma during their lifetime.

Risk factors for conversion to PXF glaucoma include the presence of PXF material (within ocular tissues and bilateral ocular involvement), ocular hypertension [36], decreased pupillary dilation [34], and the presence of pigment on the angle structures [37]. The amount of pigment present in the iridocorneal angle appears to correlate more closely with the severity and development of PXF glaucoma than the amount of PXF material present on the lens capsule [37]. Although the risk of PXF glaucoma is elevated in patients with LOXL1 SNP mutations [2, 4, 5, 7, 8, 38], how the presence of these genetic changes are associated with conversion rates to PXF glaucoma is unknown.

Recent new data suggests gene–environment interaction factors play a role in the clinical manifestation of pseudoexfoliation glaucoma. Climatic and latitude effects have been identified along with more controversial environmental factors such as vitamin D levels, coffee consumption, and dietary folate levels [39].

Summary for the Clinician

- The presentation of clinically apparent PXF material is often unilateral.
- The presence of unilateral PXF material often becomes bilateral with long-term observation.
- The presence of PXF material in the eye is a significant risk factor for ocular hypertension and the development of PXF glaucoma. Thus, patients with PXF material in the eye should be closely monitored for the development of glaucoma.
- The degree of iridocorneal angle pigmentation correlates more strongly with the development of PXF glaucoma than does the amount of PXF material on the lens capsule.

44.4 What Are Surgical Considerations and Management Issues in Cataract Extraction in the Setting of Pseudoexfoliation?

The presence of PXF material in the eye is associated with a significantly increased risk of complications during cataract surgery [10, 40]. These complications include vitreous prolapse into the anterior chamber (i.e., through sectorial areas of preexisting or iatrogenic zonular dehiscence), complete or partial lens prolapse into the vitreous cavity, and posterior capsular tears created during cataract surgery. Some of these complications are due to zonular dehiscence associated with PXF (Fig. 44.2), while others are associated with poor pupillary dilation [41] that can lead to small capsulorhexis creation and poor visualization during cataract surgery. PXF is also associated with increased iris vessel leakage and increased postoperative cell and flare after cataract surgery that may require a more prolonged course of anti-inflammatory medication treatment. PXF patients should be cautioned that their cataract surgery entails increased surgical risks. In addition, surgeons should consider that softer lenses are easier to extract with less zonular stress than more brunescent lenses, i.e., PXF cataracts are best removed earlier rather than later when they are denser.

44.4.1 Dilation of the Pseudoexfoliation Pupil

Cataract surgery is a stepwise process where preceding steps affect subsequent steps. The amount of pupillary dilatation in the clinic should be noted in the chart prior to a cataract surgery, since poor pupillary dilation is associated with PXF. If the pupil is not dilated at least to the level documented in the clinic, one

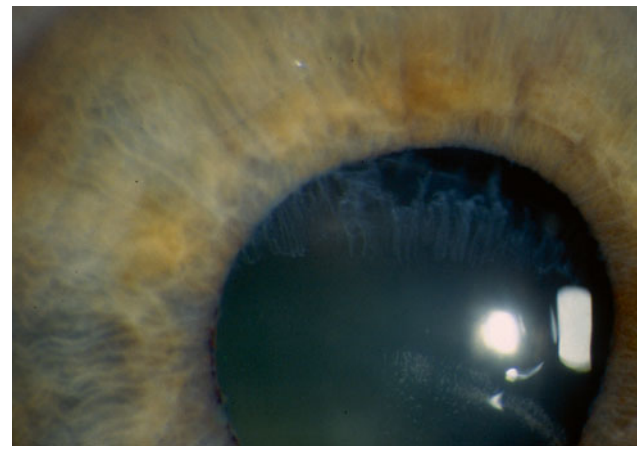

Fig. 44.2 Advanced zonular dehiscence secondary to PXF resulting in an inferiorly subluxed lens with loose zonules superiorly. Note the loss of the peripupillary ruff often associated with PXF

should give additional rounds of dilating drops to increase dilation closer to the desired size. If it is noted that the pupil does not dilate well in the clinic, instruction should be given preoperatively to have pupil-dilating instruments ready in the operating room. In addition to preoperative mydriatic eye drops, intracameral lidocaine may also pharmacologically aid in pupil dilation.

The additional dilation provided by filling the anterior chamber with viscoelastic is often adequate to obtain a reasonably sized capsulorhexis; however, surgeons need to be cautioned that with the commencement of phacoemulsification viscoelastic will be aspirated out of the eye and the pupil may return to its original smaller state. A large capsulorhexis is desired not only for maximal visualization during cataract surgery, but also to minimize postoperative capsular phimosis that can cause progressive zonular dehiscence and increase the risk of in-the-bag intraocular lens (IOL) dislocation over the patient's lifetime.

Instruments for pupil dilation include using two Kuglen or similar hooks to bimanually stretch the pupil at two diametrically opposite axes as far towards the iris base as is possible along the pupillary plane (so as not to violate the lens capsule or break zonules during pupil stretching). A more effective pupil expansion is provided by the three- or preferably the four-pronged Beehler hook that stretches the pupil open at multiple axes simultaneously [42]. If during the pupil stretching a Vossius ring is observed on the lens capsule, a small pupil may be due to iridolenticular touch and synechiae formation, thereby increasing the possibility that mechanical stretching of the pupil may be adequate to maintain a formed large pupil.

Constant pupil expansion is possible during the entire cataract extraction surgery using mechanical pupil expansion rings or iris retraction hooks. Pupil expansion rings include the Malyugin pupil expander (MST, Redmond, WA, USA), which attaches to the pupillary border in a square/diamond configuration and holds the pupil open until the ring is removed at the end of surgery. Iris retraction hooks can also be inserted (four to five are usually placed) creating a dilated pupil in a square or pentagonal configuration and are removed after completion of cataract extraction. The advantage of using pupil-dilating devices is that pupillary dilation is mechanically maintained throughout cataract surgery [42].

44.4.2 Cataract Extraction Technique

Many different techniques can be used to extract the lens nucleus, and some are less stressful to lens zonules than others. Minimal stress to the zonules is critical for successful cataract extraction in the PXF eye, which has preexisting risk for zonular dehiscence. Extra capsular cataract extraction by prolapsing the lens nucleus *en toto* from the capsular bag is a common method for removing cataracts (especially dense ones) with minimal zonular stress [43, 44]. If phacoemulsification is the preferred surgical technique, supracapsular prolapse of the lens nucleus into the iris plane and then phacoemulsification with chopping is recommended, since this technique is similar to conventional extra capsular cataract extraction. Supracapsular lens prolapse minimizes undue zonular stress because the lens nucleus is out of the capsular bag during phacoemulsification. If cataract extraction is to be performed inside the capsular bag, techniques such as cracking the lens nucleus into hemisections are preferable to standard divide-and-conquer approaches in order to minimize downward pressure on the zonules. Phacoemulsification within the capsular bag can stress and break weakened zonules. In addition, use of chopping is encouraged to minimize phacoemulsification power and time in the capsular bag.

44.4.3 Management of Zonular Dehiscence and Laxity

One of the major risk factors for surgical complications in the PXF eye is the presence or development of zonular laxity during cataract surgery. A lower bottle height and minimal entry and exit through the corneal incision will minimize the bounce and stretch on zonules that occurs when

irrigation is turned to pressurize eye. In addition, higher phacoemulsification power can be used to cut through the lens more efficiently to minimize push and pull of the lens nucleus by the phacoemulsification needle in the capsular bag.

If zonular weakness or loss is noted during cataract surgery, several mechanical devices can be used to minimize further zonular loss. Iris or capsule retraction hooks can be used to hook the capsular bag edge to minimize movement of the bag during phacoemulsification. Segmental capsular tension rings (CTR) can also be sewn into the sclera to fixate the capsular bag during phacoemulsification. One popular approach is to place a CTR to redistribute zonular stress evenly throughout the capsular bag during phacoemulsification [4, 45, 46]. However, one needs to be careful because the CTR can incarcerate cortical material. Incarceration of cortical material will make irrigation and aspiration of lens cortex more difficult and possibly may cause more zonular loss by pulling on cortex trapped between the CTR and the capsular bag. CTRs should not be placed into a compromised capsular bag as the CTR may exit the capsular bag into the vitreous cavity and then require complex vitreoretinal surgery to remove the CTR and any prolapsed lens material [47].

A CTR is most safely used in a lens capsule with less than 3 or 4 h of dehiscence and after the removal of the cortex with the posterior capsule intact. However, in this context it may be just as efficacious to use a three-piece IOL placed along the axis of zonular loss. The haptics in a three-piece IOL or four haptic one-piece IOL probably produce as much tension as a CTR to distribute stress evenly among the capsular zonules in an area of compromise. In addition, if the IOL in the capsular bag should ever dislocate into the vitreous cavity, removal of an IOL alone is much simpler than removal of an IOL with a CTR in the bag.

If significant zonular laxity is present or greater than 4 or 5 h of zonular dehiscence is noted, placement of a three-piece IOL in the sulcus is a safer option than attempting placement of an IOL in the bag. The risk of future in-the-bag IOL dislocation into the vitreous cavity is probably elevated although the factors for subsequent in-the-bag IOL dislocation are not well characterized. One should keep in mind that the newer models of anterior chamber IOLs perform remarkably well and can be easily inserted through a widened clear corneal incision. Thus, if concern exists about posterior chamber IOL dislocation in a PXF eye, placement of an anterior chamber IOL can be a good and safe option, as well as sewn-in IOLs to the iris or sclera.

44.4.4 Postoperative Surgical Care of the Pseudoexfoliation Eye

PXF eyes, even with uncomplicated cataract surgery, tend to have more postoperative cell and flare than non-PXF eyes. The increased postoperative inflammation is probably due to the increased leakage seen from iris vessels in pseudoexfoliation eyes [43, 48, 49]. A longer course and slower taper of steroids should be planned for PXF eyes to increase the patient's comfort and to decrease the risk of cystoid macular edema.

Summary for the Clinician

- Poor pupil dilation and poor zonular integrity in PXF eyes increases the risk of complications with cataract surgery.
- Cataract extraction should be considered at earlier stages in PXF eyes because less zonular stress is induced by the removal of softer nuclei.
- A sufficiently large pupil is important for maximal visualization during cataract surgery and to minimize capsular phimosis that may be associated with late in-the-bag IOL dislocation.
- Techniques that minimize zonular stress should be used in PXF eyes: extracapsular cataract extraction, phacoemulsification using supracapsular prolapse, lower bottle height during phacoemulsific,

minimizing the number of entrances and exits from the eye, and using lens chopping techniques.

- A CTR, a three-piece IOL, or a four haptic one-piece IOL may be helpful in distributing zonular stress to minimize zonular stress and loss.
- PXF eyes have more postoperative inflammation that may require a more prolonged course of anti-inflammatory treatment.

References

1. Lee RK. The molecular pathophysiology of pseudoexfoliation glaucoma. Curr Opin Ophthalmol. 2008; 19(2):95–101.
2. Thorleifsson G, et al. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science. 2007;317(5843):1397–400.
3. Yang X, et al. Genetic association of LOXL1 gene variants and exfoliation glaucoma in a Utah cohort. Cell Cycle. 2008;7(4):521–4.
4. Wiggs JL. Association between LOXL1 and pseudoexfoliation. Arch Ophthalmol. 2008;126(3):420–1.
5. Ozaki M, et al. Association of LOXL1 gene polymorphisms with pseudoexfoliation in the Japanese. Invest Ophthalmol Vis Sci. 2008;49:3976–80.
6. Hayashi H, et al. Lysyl oxidase-like 1 polymorphisms and exfoliation syndrome in the Japanese population. Am J Ophthalmol. 2008;145(3):582–5.
7. Fan BJ, et al. DNA sequence variants in the LOXL1 gene are associated with pseudoexfoliation glaucoma in a U.S. clinic-based population with broad ethnic diversity. BMC Med Genet. 2008;9:5.
8. Challa P, et al. Analysis of LOXL1 polymorphisms in a United States population with pseudoexfoliation glaucoma. Mol Vis. 2008;14:146–9.
9. Fingert JH, et al. LOXL1 mutations are associated with exfoliation syndrome in patients from the midwestern United States. Am J Ophthalmol. 2007;144(6): 974–5.
10. Schlotzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol. 2006;141(5):921–37.
11. Aung T, et al. A common variant mapping of CACNA1A is associated with susceptibility to exfoliation syndrome. Nat Genet. 2015;47:689.
12. Kuchle M, Schlotzer-Schrehardt U, Naumann GO. Occurrence of pseudoexfoliative material in parabulbar structures in pseudoexfoliation syndrome. Acta Ophthalmol (Copenh). 1991;69(1):124–30.
13. Streeten BW, et al. Pseudoexfoliative fibrillopathy in the skin of patients with ocular pseudoexfoliation. Am J Ophthalmol. 1990;110(5):490–9.
14. Streeten BW, et al. Pseudoexfoliative fibrillopathy in visceral organs of a patient with pseudoexfoliation syndrome. Arch Ophthalmol. 1992;110(12):1757–62.
15. Gillies WE, Brooks AM. Central retinal vein occlusion in pseudoexfoliation of the lens capsule. Clin Experiment Ophthalmol. 2002;30(3):176–87.
16. Shrum KR, Hattenhauer MG, Hodge D. Cardiovascular and cerebrovascular mortality associated with ocular pseudoexfoliation. Am J Ophthalmol. 2000;129(1):83–6.
17. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. Am J Ophthalmol. 1997;124(5):685–7.
18. Bojic L, et al. Pseudoexfoliation syndrome and asymptomatic myocardial dysfunction. Graefes Arch Clin Exp Ophthalmol. 2005;243(5):446–9.
19. Citirik M, et al. A possible link between the pseudoexfoliation syndrome and coronary artery disease. Eye. 2007;21(1):11–5.
20. Schumacher S, et al. Pseudoexfoliation syndrome and aneurysms of the abdominal aorta. Lancet. 2001;357(9253):359–60.
21. Tarkkanen A, Reunanen A, Kivela T. Frequency of systemic vascular diseases in patients with primary open-angle glaucoma and exfoliation glaucoma. Acta Ophthalmol. 2008;86:598–602.
22. Hietanen J, et al. Evaluation of the clinical association between exfoliation syndrome and abdominal aortic aneurysm. Acta Ophthalmol Scand. 2002;80(6):617–9.
23. Ringvold A. Pseudoexfoliation and aortic aneurysms. Lancet. 2001;357(9274):2139–40.
24. Visontai Z, et al. Increase of carotid artery stiffness and decrease of baroreflex sensitivity in exfoliation syndrome and glaucoma. Br J Ophthalmol. 2006; 90(5):563–7.
25. Irkec M. Exfoliation and carotid stiffness. Br J Ophthalmol. 2006;90(5):529–30.
26. Roedl JB, et al. Homocysteine in tear fluid of patients with pseudoexfoliation glaucoma. J Glaucoma. 2007;16(2):234–9.
27. Bleich S, et al. Elevated homocysteine levels in aqueous humor of patients with pseudoexfoliation glaucoma. Am J Ophthalmol. 2004;138(1):162–4.
28. Vessani RM, et al. Plasma homocysteine is elevated in patients with exfoliation syndrome. Am J Ophthalmol. 2003;136(1):41–6.
29. Leibovitch I, et al. Hyperhomocystinemia in pseudoexfoliation glaucoma. J Glaucoma. 2003;12(1):36–9.
30. Turacli ME, et al. Methylene tetrahydrofolate reductase 677 C-T and homocysteine levels in Turkish patients with pseudoexfoliation. Clin Experiment Ophthalmol. 2005;33(5):505–8.
31. Yazdani S, et al. Sensorineural hearing loss in pseudoexfoliation syndrome. Ophthalmology. 2008;115(3):425–9.
32. Cahill M, et al. Pseudoexfoliation and sensorineural hearing loss. Eye. 2002;16(3):261–6.
33. Hammer T, Schlotzer-Schrehardt U, Naumann GO. Unilateral or asymmetric pseudoexfoliation syndrome?

An ultrastructural study. Arch Ophthalmol. 2001;119(7):1023–31.
34. Puska PM. Unilateral exfoliation syndrome: conversion to bilateral exfoliation and to glaucoma: a prospective 10-year follow-up study. J Glaucoma. 2002;11(6):517–24.
35. Jeng SM, et al. The risk of glaucoma in pseudoexfoliation syndrome. J Glaucoma. 2007;16(1):117–21.
36. Grodum K, Heijl A, Bengtsson B. Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. Ophthalmology. 2005;112(3):386–90.
37. Shuba L, Nicolela MT, Rafuse PE. Correlation of capsular pseudoexfoliation material and iridocorneal angle pigment with the severity of pseudoexfoliation glaucoma. J Glaucoma. 2007;16(1):94–7.
38. Pasutto F, et al. Association of LOXL1 common sequence variants in German and Italian patients with pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Invest Ophthalmol Vis Sci. 2008;49(4):1459–63.
39. Pasquale LR, Kang JH, Wiggs JL. Consideration for gene-environment interactions as novel determinants of exfoliation syndrome. Int Ophthalmol Clin. 2014;54(4):29–41.
40. Conway RM, et al. Pseudoexfoliation syndrome: pathological manifestations of relevance to intraocular surgery. Clin Experiment Ophthalmol. 2004;32(2):199–210.
41. Asano N, Schlotzer-Schrehardt U, Naumann GO. A histopathologic study of iris changes in pseudoexfoliation syndrome. Ophthalmology. 1995;102(9):1279–90.
42. Akman A, et al. Comparison of various pupil dilatation methods for phacoemulsification in eyes with a small pupil secondary to pseudoexfoliation. Ophthalmology. 2004;111(9):1693–8.
43. Drolsum L, Haaskjold E, Davanger M. Results and complications after extracapsular cataract extraction in eyes with pseudoexfoliation syndrome. Acta Ophthalmol (Copenh). 1993;71(6):771–6.
44. Drolsum L, Haaskjold E, Davanger M. Pseudoexfoliation syndrome and extracapsular cataract extraction. Acta Ophthalmol (Copenh). 1993;71(6):765–70.
45. Sun R. Functions of the capsular tension ring. J Cataract Refract Surg. 2007;33(1):4.
46. Hasanee K, Ahmed II. Capsular tension rings: update on endocapsular support devices. Ophthalmol Clin North Am. 2006;19(4):507–19.
47. Ahmed II, et al. Surgical repositioning of dislocated capsular tension rings. Ophthalmology. 2005;112(10):1725–33.
48. Kuchle M, et al. The blood-aqueous barrier in eyes with pseudoexfoliation syndrome. Ophthalmic Res. 1995;27 Suppl 1:136–42.
49. Kuchle M, et al. Quantitative assessment of aqueous flare and aqueous “cells” in pseudoexfoliation syndrome. Acta Ophthalmol (Copenh). 1992;70(2):201–8.

Glaucomas: Pigment Dispersion Syndrome, Pigmentary Glaucoma, and Angle Recession Glaucoma

45

Carlos Gustavo De Moraes and Remo Susanna Jr.

Core Messages

- Pigmentary glaucoma (PG) has particular features that affect its clinical management. Outcomes tend to be similar to other types of glaucoma with similar treatments.
- Patients with pigment dispersion syndrome have about a 10 % risk of converting to PG at 5 years and 15 % at 15 years.
- Patients with angle recession may respond poorly to standard medical and surgical treatment and final visual outcomes may be influenced by other ocular complications. Long-term follow-up is important as a certain percentage of angle recession patients can develop elevated IOP and glaucoma more than 10 years following initial injury.

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45.1 How Does Glaucoma in Pigment Dispersion Syndrome Differ Clinically from Other Glaucomas?

Pigment dispersion syndrome (PDS) is a clinical entity characterized by the release of pigment granules throughout the anterior segment that has been attributed to friction between the posterior iris surface and the anterior zonular bundles [1]. Decreased outflow facility due to PDS may lead to increased intraocular pressure (IOP) and glaucomatous optic neuropathy (GON), which characterize pigmentary glaucoma (PG).

PDS is often described as an autosomal dominant disorder with variable penetrance [2]. Although PDS often shows a familial aggregation, its inheritance does not usually follow Mendelian family patterns. Rather, it seems to be caused by multiple genes usually interacting with various environmental factors. The phenotype may result from combinations of mutations in more than one gene or from common variants in many genes, each contributing small effects. A single susceptibility locus to PDS has been mapped on chromosome 7q35–q36 but the candidate gene is yet to be identified [3]. PDS is more common among young myopic males (between 30 and 40 years old) of white ethnicity with a positive family history. Usually both eyes are involved, although the disease may be

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asymmetric. The amount of pigment observed during slit-lamp examination has not been correlated to the risk of converting to PG [4].

Clinically, the hallmarks of PG are the Krukenberg spindle (fine pigment granules on the corneal endothelium) (Fig. 45.1), slit like radial midperipheral iris transillumination defects (Fig. 45.2), and increased pigmentation of the trabecular meshwork (Fig. 45.3). Other findings include the presence of a pigmented line on the juxtazonular posterior capsule (Scheie stripe) (Fig. 45.4), pigment on the anterior and posterior lens capsule near the equator (Zentmayer's ring) (Fig. 45.5), and prominent reverse convexity of the peripheral iris. Sampaolesi has also described a more posterior insertion of the iris root observed on gonioscopy [5]. PG patients show an increased risk of rhegamatogenous retinal detachment (between 4 and 6 % in 10 years) when compared to normal myopic individuals [4, 6]; thus, ophthalmologic examination in these patients should include careful fundoscopic examination of the peripheral retina. Histological studies have demonstrated the presence of increased pigment granules in Schlemm's canal of PG patients [7], which may play a role in the genesis of the disease. Imaging techniques have demonstrated an increased posterior iris convexity that results in abnormal contact between the iris periphery and the zonular bundles (reverse pupillary block) [2, 8] (Fig. 45.6).

Fig. 45.1 Krukenberg spindle: fine pigment granules on the corneal endothelium (Courtesy of Robert Ritch, M.D.)

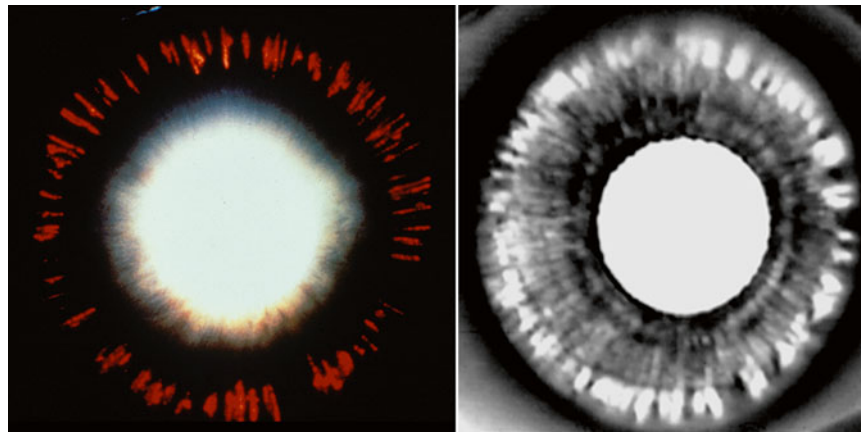

Fig. 45.2 Iris transillumination defects in pigment dispersion syndrome (Courtesy of Robert Ritch, M.D.)

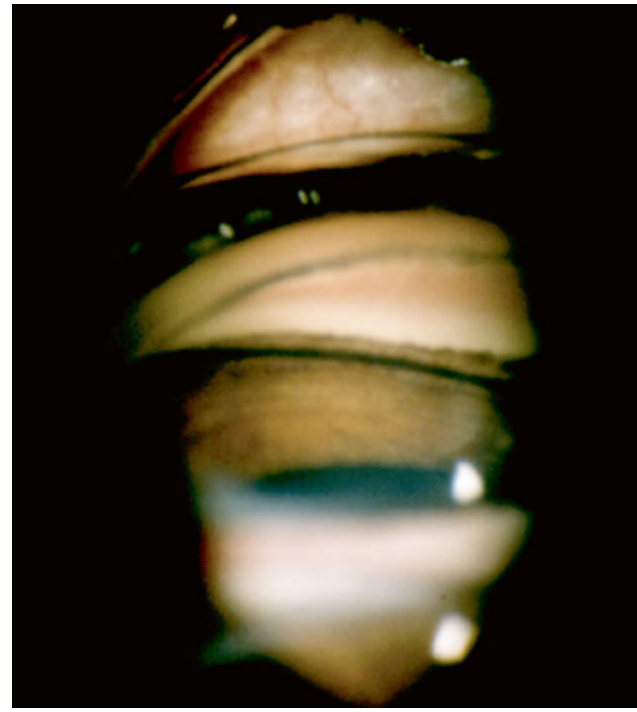

Fig. 45.3 Increased trabecular pigmentation in pigment dispersion syndrome (Courtesy of Robert Ritch, M.D.)

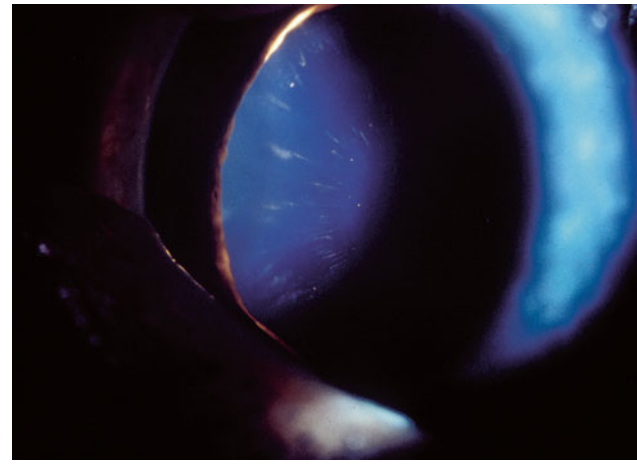

Fig. 45.4 Scheie stripe: pigmented line posterior to the lens capsule (Courtesy of Robert Ritch, M.D.)

PG patients show higher IOP peaks than PDS individuals with ocular hypertension during 24 h tension curves [9]. In 1956 Becker and Podos found abnormal results in PDS patients during the water drinking test (WDT) and tonography, as well as a high responsiveness to topical steroids [10]. It has been reported that the number of aqueous melanin granules is strongly correlated with the peak IOP during 24-h curves in eyes with or without mydriasis [9], which supports the relationship between aqueous melanin dispersion and development of PG. In patients undergoing pharmacologic mydriasis, maximal pigment liberation occurred immediately after maximal dilation, although the IOP continued to elevate for at least 1.5 h thereafter [11]. Significant

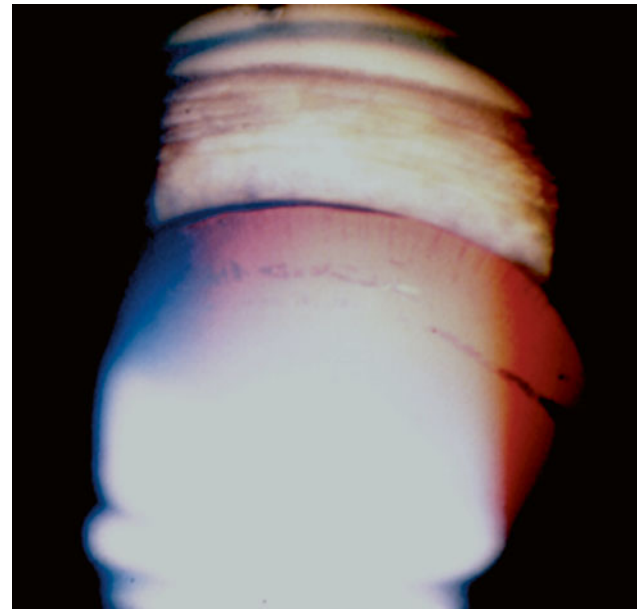

Fig. 45.5 Zentmayer ring: pigment on the posterior lens capsule near the equator (Courtesy of Robert Ritch, M.D.)

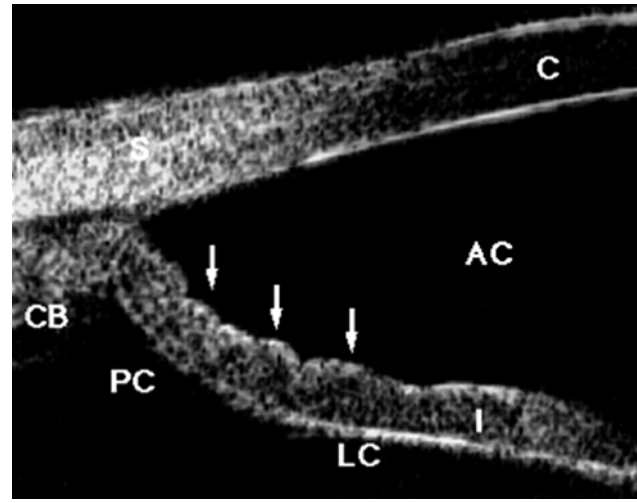

Fig. 45.6 Iris backbowing seen during ultrasound biomicroscopic examination in an eye with pigmentary glaucoma (Courtesy of Robert Ritch, M.D.)

pigment release and IOP spikes can occur following moderate to extensive physical activity in these patients, although its effect on the risk of glaucoma onset or progression remains unclear.

Patients with PDS have a 10 % risk of converting to glaucoma at 5 years and 15 % at 15 years [12]. Although the prevalence of PG is higher among young myopic males, the only significant predictor of conversion to glaucoma among PDS patients is an IOP greater than 21 mmHg at baseline assessment [12].

Summary for the Clinician

- Pigment released into the anterior chamber causes decreased outflow facility.
- The amount of pigment observed at the slit-lamp does not correlate to the risk of converting to PG.
- PG patients show an increased risk of rhegamatogenous retinal detachment.

- PG patients have higher IOP peaks and greater IOP fluctuation than POAG patients.
- PDS patients have a 10 % risk of converting to PG at 5 years and 15 % risk at 15 years.

45.2 Is PG Managed Differently Than Primary Open-Angle Glaucoma?

45.2.1 Medical Treatment

Initial treatment involves IOP reduction using topical IOP-lowering medications. Most medication classes can be used in PG patients and an IOP reduction similar to that seen in POAG patients is expected. Care should be taken while using cholinergic agents in these patients because of their increased risk of retinal detachment (see Sect. 45.4).

45.2.2 Trabeculoplasty

Argon laser trabeculoplasty (ALT) has been shown to be an effective procedure with higher success rates in PG patients than in other types of open-angle glaucoma. Ritch and colleagues found a cumulative success rate of 80 % at 1 year, 62 % at 2 years, and projected 45 % at 3 years [13]. Since the increased pigmentation of the trabecular meshwork allows greater absorption of energy, it is advisable to use lower energy settings during the procedure in order to avoid trabecular damage, peripheral anterior synechiae, and subsequent permanent IOP elevation.

Selective laser trabeculoplasty (SLT) appears to have a similar success rate in PG as ALT. In PG eyes undergoing 180° of SLT, Ayala showed that the average time to failure was 27 months. The success rates after 1, 2, 3 and 4 years were 85 %, 67 %, 44 %, and 14 %, respectively [14].

45.2.3 Trabeculectomy

If the target IOP range is not reached despite maximally tolerated medical therapy, trabeculectomy with or without adjunctive use of antifibrotic agents may be indicated.

The Trabeculectomy Study Group (TSG) found that PG is one predictor of treatment success; 77 % of eyes in this study showed an IOP between 6 and 16 mmHg with 1 year of follow-up [15]. The National Survey of Trabeculectomy also found good success rates with PG [16]. One should consider that young patients tend to show more intense conjunctival scarring and have longer life expectancy than older patients, which increases the chances of bleb failure during their lifetime. This should be taken into account when performing trabeculectomy in PG eyes, since these patients are usually younger than those with POAG and may require multiple incisional procedures during their lifespan.

In our experience, trabeculectomy in PG results in significant and longstanding IOP control with success rates similar to those found in other types of OAG. We recommend the use of antifibrotic agents (mitomycin-C or 5-fluorouracil) during trabeculectomy in PG patients to prevent conjunctival scarring and allow long-standing IOP control (Table 45.1).

Summary for the Clinician

- Any topical medication can be used to control IOP but precaution should be taken with miotics.
- Trabeculoplasty has been shown to be highly effective in PG.
- Filtration surgery may be required more frequently in PG patients.
- Trabeculectomy success rates are equal between PG and POAG.

Table 45.1 Clinical and surgical differences between primary open-angle glaucoma (POAG) and pigmentary glaucoma (PG)

Characteristics	POAG	PG
Age	>45	30–40
Gender/ethnicity	Both/greater prevalence among Blacks	Male/White
IOP profile	Greater fluctuation and peaks than normal	Greater fluctuation and peaks than POAG
Gonioscopy	Open angle	Open angle, intense pigmentation
Biomicroscopy	Deep anterior chamber	Deep anterior chamber, Krukenberg spindle, Scheie stripe, Zentmayer ring
ALT response	+	++
Trabeculectomy response	+	+, Slightly better than POAG, greater risk of hypotony

45.3 Is Laser Iridotomy Recommended in PDS/PG Patients?

Reverse pupillary block is a term used to describe the iris-lens configuration seen in PDS/PG in which the peripheral iris bows backwards towards the lens. Some studies have suggested that peripheral laser iridotomy relieves the reverse pupillary block and flattens the peripheral iris, decreasing its friction with the zonular bundles [17–19], thereby halting the pathogenesis of anterior segment pigment dispersion. In a prospective study, Gandolfi and coworkers found that peripheral laser iridotomy reduced the incidence of ocular hypertension in eyes affected by PDS although this effect was less pronounced after 40 years of age [20]. On the other hand, the American Glaucoma Society Pigmentary Glaucoma Iridotomy Study Group (AGS-PGISG) did not find support for the benefit of laser peripheral iridotomy in the long-term IOP control of patients with PG [21]. In their 10-year follow-up study, Gandolfi and coworkers showed that approximately one-third of the PDS patient population undergoing laser iridotomy demonstrated an IOP increase of 5 mmHg or higher in at least 1 eye at some point during follow-up. They also found that phenylephrine-provocative testing identified eyes at high-risk for developing IOP elevation and that laser iridotomy reduced the rate of IOP elevation among high-risk eyes to the same level as the low-risk group [22]. Nonetheless, in another prospective, randomized, controlled trial there was no benefit of laser iridotomy in preventing progression from PDS with ocular hypertension to PG within 3 years of follow-up [23]. The occurrence of significant IOP spikes has been described following the procedure [24], and to the best of our knowledge, there is still no consensus supporting the use of laser iridotomy as a routine procedure in PDS or PG patients either for prevention or treatment.

Summary for the Clinician

- There is currently no consensus supporting the routine use of laser iridotomy in PDS/PG. There is conflicting evidence in the literature as to the long-term benefit of laser iridotomy in PDS/PG.
- In one study the effect of laser iridotomy was less pronounced when used in patients older than 40 years.

45.4 What Problems Should Be Anticipated in PDS/PG? What Kind of Outcomes Can Be Expected in These Patients?

One should anticipate large IOP fluctuations throughout follow-up, despite compliance with treatment. Pupil dilation or moderate exercise may increase pigment release into the anterior chamber and cause IOP spikes. Some patients with GON may present with low IOP after long periods of elevated pressures. The low IOP may be due to the pigment release process "burning out" because of an unexplained reduction of posterior iris friction and improvement of the outflow facility.

These patients have a higher rate of steroid-responsiveness and so care should be taken in situations when steroids are necessary, such as following blunt trauma or intraocular surgery. Preferably, topical steroids should be used for short periods or may be switched to agents that are less likely to elevate the IOP. One should anticipate peripheral retinal problems such as tears or degenerations. During follow-up, routine indirect ophthalmoscopy of the peripheral retina is advisable and topical anti-cholinergic agents should be avoided.

In PG patients undergoing trabeculectomy, one must be aware that these patients tend to be young myopic males who have an increased risk of postoperative hypotony, as demonstrated by previous publications [25–27]. Fannin found a trend for hypotony maculopathy in eyes with PG [25]. During trabeculectomy in PG eyes, we recommend avoiding thin scleral flaps, cautious use of mitomycin-C, tight scleral flap sutures, and cautious postoperative laser suture lysis to prevent chronic hypotony.

Summary for the Clinician

- PG patients may have large IOP fluctuations despite adherence to prescribed medication regimens.
- PG can present with low IOP after the disease "burns itself out" and outflow facility improves.
- PG patients experience a higher rate of steroid-responsiveness.
- Young PG patients may experience a higher rate of hypotony maculopathy after trabeculectomy.

45.5 How Does Glaucoma in Angle Recession Differ from Other Glaucomas?

Blunt ocular trauma may lead to anatomical cleavage of the circular and radial ciliary muscle bundles, which can be seen on gonioscopic examination as retrodisplacement of the iris root (Fig. 45.7) [28–30]. The association between such anatomical changes and elevated IOP has been called angle recession glaucoma (ARG) [31]. The anatomical deformity itself is probably not responsible for the development of elevated IOP and glaucoma [32]. Rather, the observed gonioscopic findings may reflect histopathologic injury sustained by the trabecular meshwork ultrastructure, which then leads to increased aqueous humor outflow resistance. Of note, there is a strong correlation between anterior chamber hemorrhage acutely following injury and angle recession; 56–100 % of patients with traumatic hyphema have been reported to have some degree of angle recession [29, 33–36].

Fig. 45.7 Gonioscopic view of angle recession. An increased band of pigmented tissue (ciliary muscle) is present posterior to the scleral spur (Courtesy of Sung Chul Park, M.D.)

Elevated IOP and glaucoma may have an early or late onset following angle recession. Acutely following blunt trauma, anterior segment inflammation and hyphema play a more prominent role in IOP elevation, which generally returns to baseline levels after 4–6 weeks of medical treatment. However, approximately 9 % of patients with recession involving 180° or more of the angle will develop glaucoma over long-term follow-up [36, 37]. In a 10-year prospective follow-up study of 31 eyes with angle recession, 6 % developed glaucoma [36]. In a retrospective review of 130 cases of angle recession, nine eyes (7 %) developed glaucoma—five received glaucoma diagnoses within 3 years of injury and four received diagnoses 10 or more years later [29]. Herschler found that 16.5 years elapsed between blunt trauma and glaucoma diagnosis [32]. A number of authors have noted two peak incidences of glaucoma after angle recession. The first peak occurs within 3 years and the second 10 or more years following injury [38]. Fortunately, not everyone with angle recession develops glaucoma. If there is less than 180° of angle involved it is unlikely that glaucoma will develop, but if 180–360° are involved there is a higher likelihood of late-onset glaucoma [39]. Moreover, the fellow eyes of patients with unilateral angle recession show an increased risk of developing OAG during follow-up. These fellow eyes also show an abnormal IOP elevation with topical steroids, despite no previous history of ocular injury, which suggests an underlying tendency to develop OAG in this group of patients that goes on to develop glaucoma after angle recession [34].

Summary for the Clinician

- Gonioscopic findings in angle recession reflect histopathologic injury to the trabecular meshwork.
- There is a strong correlation between anterior chamber hemorrhage acutely following injury and angle recession.
- Approximately 9 % of patients with angle recession will go on to develop glaucoma.
- There are two peak incidences for ARG—within 3 years of injury and a later onset after 10 years.
- Greater than 180° of angle recession makes it more likely that ARG will develop.

45.6 What Are the Expected Medical, Laser, and Surgical Treatment Outcomes in Angle Recession Glaucoma?

45.6.1 Medical Therapy

Elevated IOP in eyes with ARG can be successfully controlled with most classes of IOP-lowering medications. In some cases caution with prostaglandin analogues is warranted as they may exacerbate preexisting intraocular inflammation. Miotics may be ineffective due to disruption of the normal ciliary muscle/scleral spur relationship [39] and paradoxic elevations have been reported [40]. Also, complex drug regimens may lead to low adherence, especially in younger patients who do not perceive the future risk of vision loss.

45.6.2 Laser and Incisional Surgery

When medical therapy is insufficient or not tolerated, surgical treatment may be necessary. Options include laser or incisional surgery. However, ALT is usually not effective in ARG [41, 42]. Thus, trabeculectomy may be necessary in order to halt glaucomatous damage. There are few published studies with high-level of evidence examining surgical outcomes in ARG, although some data primarily on black and mixed race younger males provide some insight. In a retrospective case–control design study matching 35 consecutive South African ARG patients to 35 POAG patients, Mermoud et al. reported that traumatic angle recession is a risk factor for bleb failure after trabeculectomy

[43]. Of note, trabeculectomies in this study were performed *without* antifibrotic agents. With success defined as IOP ≤ 21 mmHg, bleb failure was twice as likely in ARG patients over 22 months of follow-up (57 % vs. 26 % in POAG) and occurred earlier in the ARG group (mean 3.1 vs. 9.4 months). In another retrospective study examining results of trabeculectomy with mitomycin-C in 43 consecutive eyes with ARG, survival curves predicted mitomycin trabeculectomy success of 85 % at 1 year and 66 % at 3 years [44], which appears to be better than in the study without the use of mitomycin. In a third retrospective report comparing trabeculectomy without antimetabolite, trabeculectomy with mitomycin-C, and single plate Molteno tube implantation, the trabeculectomy with mitomycin-C group was found to have the highest rate of IOP control. The Molteno tube group had a 56 % success rate within 1 year of follow-up, equal to that of the trabeculectomy without antimetabolite group [33]. The results of these studies cannot be generalized to other ethnic groups or different age groups, which may respond differently to incisional surgery.

The relatively high risk of glaucoma filtering surgery failure in ARG patients may in part be attributed to early activation of fibroblast proliferation that is observed in young patients with a history of ocular inflammation [43]. We recommend the use of wound healing modulators (mitomycin-C) during trabeculectomy in eyes with ARG. These eyes may even need additional subconjunctival injections of antifibrotic agents (5-fluorouracil) postoperatively to prevent early bleb scarring.

Summary for the Clinician

- Miotics may be ineffective in ARG and prostaglandin analogues may be relatively contraindicated if there is inflammation.
- Laser trabeculoplasty is usually not effective in ARG.
- There is little literature on surgical outcomes in ARG
- Patients with ARG are usually younger than the average OAG patient and often present with eye inflammation, which can affect the outcomes of filtering surgery.

45.7 What Problems Should Be Anticipated in Patients with Angle Recession?

Patients with a history of blunt ocular trauma, even if in the distant past, should always receive gonioscopic examination because of the high prevalence of angle recession following such injuries. Sixty to 94 % of patients with a history of blunt ocular trauma show some degree of angle recession or trabecular injury when evaluated gonioscopically [29, 30, 45, 46] (Fig. 45.7).

During initial ophthalmic evaluation, the clinician should search for other sight-threatening signs of intraocular injury: lens dislocation, traumatic cataract, inflammation, hyphema, vitreous hemorrhage, and retinal detachment. Campbell has described seven tissue rings where tears may occur following blunt ocular trauma that should be evaluated carefully [47]: (1) the sphincter pupillae, (2) the anterior ciliary body, (3) the iris root, (4) the ciliary attachment to the scleral spur, (5) the lens zonules, (6) the trabecular meshwork, and (7) the retinal attachment to the ora serrata. Specific therapy for each disorder should be promptly initiated and coupled with glaucoma treatment.

Angle recession should not be confused with cyclodialysis. The latter occurs due to an anatomical cleavage between the scleral spur and the ciliary body, often resulting in early ocular hypotony. Gonioscopically, it is characterized by a broad band of white tissue (sclera) between the trabecular meshwork and the ciliary muscle (Fig. 45.8).

The clinician should be aware that both medical and surgical therapies are often unsuccessful in ARG. Inflammation and other coexisting eye

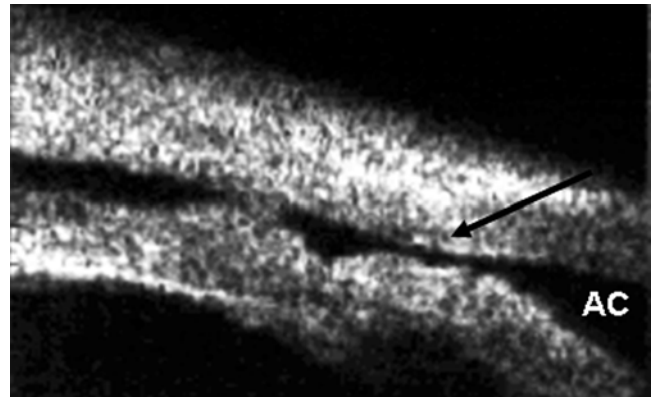

Fig. 45.8 Slit-lamp optical coherence tomography image showing an area of cyclodialysis (*arrow*). *AC* anterior chamber (Courtesy of Tiago Prata, M.D.)

disorders may demand adjunctive topical therapy (e.g., steroids) or surgery (e.g., lens extraction, vitrectomy), which can make glaucoma management more difficult. Multiple surgeries in eyes with significantly impaired vision may require cyclodestructive procedures as an end stage treatment.

Finally, patients with angle recession who have not yet developed IOP elevation should be instructed to return periodically for complete ophthalmic evaluation because of an increased risk of late-onset IOP elevation and glaucoma development in both eyes.

Summary for the Clinician

- Complete ocular evaluation, including gonioscopy, is mandatory in patients with blunt ocular trauma, even if it occurred in the distant past.
- 60–94 % of patients who relate a history of blunt ocular trauma will have angle recession.
- Concomitant disorders should be treated promptly and multiple intraocular procedures are often necessary.
- Patients with angle recession should be told that glaucoma can develop 10 or more years after an injury and therefore they need periodic examination.

References

1. Campbell DG. Pigmentary dispersion and glaucoma: a new theory. Arch Ophthalmol. 1979;97:1667–72.
2. Kanadani FN, Dorairaj S, Langlieb AM, Shihadeh WA, Tello C, Liebmann JM, Ritch R. Ultrasound biomicroscopy in asymmetric pigment dispersion syndrome and pigmentary glaucoma. Arch Ophthalmol. 2006;124(11):1573–6.
3. Andersen JS, Pralea AM, del Bono EA, Haines JL, Gorin MB, Schuman JS, Mattox CG, Wiggs JL. A gene responsible for the pigment dispersion syndrome maps to 7q35-q36. Arch Ophthalmol. 1997;115:384–8.
4. Scheie HG, Cemeron JD. Pigment dispersion syndrome: the clinical study. Br J Ophthalmol. 1981;65:264–9.
5. Sampaolsei R. Le glaucome dit pigmentaire; son rapport avec le glaucoma congenital. Bull Mem Son Fr Ophthal. 1968;81:434–63.
6. Brachet A, Chermet M. Association de glaucome pigmentaire et decollement de retine. Ann Ocul. 1974;207:451–7.
7. Gottanka J, Johnson DH, Grehn F, Lütjen-Drecoll E. Histologic findings in pigment dispersion syndrome and pigmentary glaucoma. J Glaucoma. 2006;15(2):142–51.
8. Detry-Morel ML, Van Acker E, Pourjavan S, Levi N, De Potter P. Anterior segment imaging using optical coherence tomography and ultrasound biomicroscopy in secondary pigmentary glaucoma associated with in-the-bag intraocular lens. J Cataract Refract Surg. 2006;32(11):1866–9.
9. Mardin CY, Küchle M, Nguyen NX, Martus P, Naumann GO. Quantification of aqueous melanin granules, intraocular pressure and glaucomatous damage in primary pigment dispersion syndrome. Ophthalmology. 2000;107(3):435–40.
10. Becker B, Podos SM. Krukenberg's spindles and primary open angle glaucoma. Arch Ophthalmol. 1956;76:635–9.

11. Jewelewicz DA, Radcliffe NM, Liebmann J, Ritch R. Temporal evolution of intraocular pressure elevation after pupillary dilation in pigment dispersion syndrome. J Glaucoma. 2009;18(3):184–5.
12. Siddiqui Y, Ten Hulzen RD, Cameron JD, Hodge DO, Johnson DH. What is the risk of developing pigmentary glaucoma from pigment dispersion syndrome? Am J Ophthalmol. 2003;135(6):794–9.
13. Ritch R, Liebmann J, Robin A, Pollack IP, Harrison R, Levene RZ, Hagadus J. Argon laser trabeculoplasty in pigmentary glaucoma. Ophthalmology. 1993;100(6):909–13.
14. Ayala M. Long-term outcomes of selective laser trabeculoplasty (SLT) treatment in pigmentary glaucoma patients. J Glaucoma. 2014;23(9):616–9.
15. Grehn F, Holló G, Khaw P, Overton B, Wilson R, Vogel R, Smith Z, CAT-152 Trabeculectomy Study Group. Factors affecting the outcome of trabeculectomy: an analysis based on combined data from two phase III studies of an antibody to transforming growth factor beta2, CAT-152. Ophthalmology. 2007;114(10):1831–8.
16. Edmunds B, Bunce CV, Thompson JR, Salmon JF, Wormald RP. Factors associated with success in first-time trabeculectomy for patients at low risk of failure with chronic open-angle glaucoma. Ophthalmology. 2004;111(1):97–103.
17. Breingan PJ, Esaki K, Ishikawa H, Liebmann JM, Greenfield DS, Ritch R. Iridolenticular contact decreases following laser iridotomy for pigment dispersion syndrome. Arch Ophthalmol. 1999;117(3):325–8.
18. Schwenn O, Shah B, Vogel A, Yun SH. Nd-YAG laser iridotomy in pigment dispersion syndrome and pigment dispersion glaucoma. Ophthalmologe. 2003;100(5):406–10.
19. Shuttleworth GN. A traumatic "peripheral iridotomy" protects against pigment dispersion and glaucoma. Br J Ophthalmol. 1999;83(3):376.
20. Gandolfi SA, Vecchi M. Effect of a YAG laser iridotomy on intraocular pressure in pigment dispersion syndrome. Ophthalmology. 1996;103(10):1693–5.
21. Reistad CE, Shields MB, Campbell DG, Ritch R, Wang JC, Wand M, American Glaucoma Society Pigmentary Glaucoma Iridotomy Study Group. The influence of peripheral iridotomy on the intraocular pressure course in patients with pigmentary glaucoma. J Glaucoma. 2005;14(4):255–9.
22. Gandolfi SA, Ungaro N, Tardini MG, Ghirardini S, Carta A, Mora P. A 10-year follow-up to determine the effect of YAG laser iridotomy on the natural history of pigment dispersion syndrome: a randomized clinical trial. JAMA Ophthalmol. 2014;132(12):1433–8.
23. Scott A, Kotecha A, Bunce C, Balidis M, Garway-Heath DF, Miller MH, Wormald R. YAG laser peripheral iridotomy for the prevention of pigment dispersion glaucoma a prospective, randomized, controlled trial. Ophthalmology. 2011;118(3):468–73.
24. Birt CM. Intraocular pressure spike after YAG iridotomy in patients with pigment dispersion. Can J Ophthalmol. 2004;39(3):234–9.
25. Fannin LA, Schiffman JC, Budenz DL. Risk factors for hypotony maculopathy. Ophthalmology. 2003;110:1185–91.
26. Stamper RL, McMenemy MG, Lieberman MF. Hypotonous maculopathy after trabeculectomy with subconjunctival 5-fluorouracil. Am J Ophthalmol. 1992;114:544–53.
27. Suner IJ, Greenfield DS, Miller MP, et al. Hypotony maculopathy after filtering surgery with mitomycin C: incidence and treatment. Ophthalmology. 1997;104:207–14, discussion 214–5.
28. Alper MG. Contusion angle deformity and glaucoma: gonioscopic observation and clinical course. Arch Ophthalmol. 1963;69:455–67.
29. Blanton FM. Anterior chamber angle recession and secondary glaucoma: a study of the after effects of traumatic hyphemas. Arch Ophthalmol. 1964;72:39–43.
30. Mooney D. Angle recession and secondary glaucoma. Br J Ophthalmol. 1973;57:608–12.
31. Wolff SM, Zimmerman LE. Chronic secondary glaucoma: associated with retrodisplacement of iris root and deepening of the anterior chamber angle secondary to contusion. Am J Ophthalmol. 1962;54:547–63.
32. Herschler J. Trabecular damage due to blunt anterior segment injury and its relationship to traumatic glaucoma. Trans Sect Ophthalmol Am Acad Ophthalmol Otolarygol. 1977;83:239–48.
33. Mermoud A, Salmon JF, Barron A, et al. Surgical management of post-traumatic angle recession glaucoma. Ophthalmology. 1993;100(5):634–42.
34. Spaeth GL. Traumatic hyphema, angle recession, dexamethasone hypertension, and glaucoma. Arch Ophthalmol. 1967;78(6):714–21.
35. Tonjum AM. Intraocular pressure and facility outflow late after ocular contusion. Acta Ophthalmol. 1968;46:886–908.
36. Kaufman J, Tolpin D. Glaucoma after traumatic angle recession glaucoma. Am J Ophthalmol. 1974;78:648–54.
37. Sampaolesi. Glaucoma postraumatico. In: Glaucoma. Buenos Aires: Panamericana; 1974.
38. Tumbocon JA, Latina MA. Angle recession glaucoma. Int Ophthalmol Clin. 2002;42:69–78.
39. Pilger IS, Khwarg SG. Angle recession glaucoma: review and two case reports. Ann Ophthalmol. 1985;17:197–9.
40. Bleiman BS, Schwartz AL. Paradoxical intraocular pressure response to pilocarpine: a proposed mechanism and treatment. Arch Ophthalmol. 1979;97:1305–6.
41. Fukuchi T, Iwata K, Sawaguchi S, et al. Nd:YAG laser trabeculopuncture (YLT) for glaucoma with traumatic angle recession. Graefes Arch Clin Exp Ophthalmol. 1993;231(10):571–6.

42. Melamed S, Ashkenazi I, Gutman I, et al. Nd:YAG laser trabeculopuncture in angle-recession glaucoma. Ophthalmic Surg. 1992;23(1):31–5.
43. Mermoud A, Salmon JF, Straker C, et al. Post-traumatic angle recession glaucoma: a risk factor for bleb failure after trabeculectomy. Br J Ophthalmol. 1993;77(10):631–4.
44. Manners T, Salmon JF, Barron A, et al. Trabeculectomy with mitomycin C in the treatment of post-traumatic angle recession glaucoma. Br J Ophthalmol. 2001; 85(2):159–63.
45. Canavan YM, Archer DB. Anterior segment consequences of blunt ocular injury. Br J Ophthalmol. 1982;66(9):549–55.
46. Tönjum AM. Gonioscopy in traumatic hyphema. Acta Ophthalmol (Copenh). 1966;44(4):650–64.
47. Campbell DG. Traumatic glaucoma. In: Shingleton BJ, Hersh OS, Kenyon KR, editors. Eye trauma. St. Louis: Mosby; 1991.

Glaucomas: Sturge-Weber Syndrome

46

Annette Giangiacomo and Anne L. Coleman

Core Messages

- Glaucoma in Sturge-Weber Syndrome (SWS) differs from other types of glaucoma in terms of presentation and management.
- Angle abnormalities and elevated episcleral venous pressure are responsible for glaucoma in SWS.
- The success of various treatments may depend on the age at which glaucoma develops (early childhood vs. late childhood or adulthood).
- Ocular surgery in SWS patients is associated with a greater risk of choroidal effusion or expulsive hemorrhage. There are techniques to reduce these risks.

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46.1 How Does Glaucoma in Sturge-Weber Syndrome Differ Clinically from Other Glaucomas?

Not only is Sturge-Weber syndrome (SWS) associated with intracranial and facial angiomas (nevus flammeus, see Fig. 46.1), it can also be associated with several anomalous ocular features. Most frequently, hemangiomas of the lid, episclera or conjunctiva (see Fig. 46.2), iris or ciliary body are present. Less common features include iris hyperchromia, iris neovascularization, tortuous retinal vessels (see Fig. 46.3), scleral melanosis, strabismus, and homonomyous hemianopsia because of cerebral hemangiomas. Anderson's rule says that when a hemangioma involves the upper lid, there is ipsilateral intraocular involvement. SWS is a disorder of neural crest cells, also known as encephalotrigeminal angiomatosis. The facial cutaneous angioma is usually unilateral, present at birth, and distributed over the first and second divisions of the trigeminal nerve. However, it can be bilateral in 10–30 % of the cases. Meningeal hemangiomas are associated with progressive calcification of arteries and cerebral cortex resulting in mental defects in 60 %, seizures in 85 %, and reduced life expectancy [14]. SWS has no race or sex predilection and no hereditary pattern has been established. The

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onset of glaucoma in SWS ranges from early childhood to adulthood.

Choroidal hemangiomas are present in 30–55 % of individuals with SWS [2], and of all choroidal hemangiomas 50 % are associated with SWS. These lesions tend to be flat, diffusely involve the posterior pole, and are termed "tomato catsup" fundus. These hemangiomas significantly increase the risk of intraoperative complications.

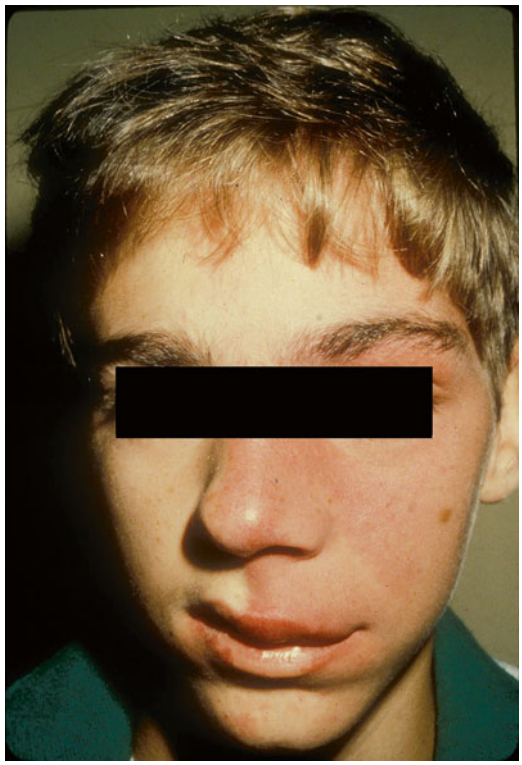

Fig. 46.1 Nevus flammeus on the *left side* of the face. Photo courtesy of Jonathan Dutton

Glaucoma occurs in 30–70 % of individuals with SWS [11, 15, 16], and it seems that patients with upper eyelid involvement are more likely to develop glaucoma [8]. When the facial angioma is unilateral, glaucoma is nearly always unilateral and ipsilateral. When individuals with SWS have glaucoma, the onset is before 2 years of age in 60 % while the remaining 40 % develop glaucoma later in childhood or in adulthood.

There are two main theories to explain the development of glaucoma in SWS—anterior chamber angle anomalies and elevated episcleral venous pressure. These anomalies have been studied histologically. The angle in SWS may be similar to that seen in primary infantile glaucoma [2] with a poorly developed scleral spur, thickened uveal meshwork, anteriorly inserted iris root onto the base of the trabecular meshwork, iris stroma covering trabecular meshwork, prominent iris processes, abnormalities of Schlemm's canal, persistent embryonic mesodermal tissue, and abnormal juxtacanalicular connective tissue. These abnormalities are thought to cause congenital or early-onset glaucoma in SWS. Those with early-onset glaucoma have the typical features of congenital glaucoma including buphthalmos, anisometropia, amblyopia, and advanced optic nerve cupping. In individuals with later-onset glaucoma, the angle may be minimally affected or appear normal. In juvenile-onset SWS glaucoma [6] investigators have reported premature aging of the angle tissues, including aging changes of the trabecular meshwork–Schlemm's canal complex

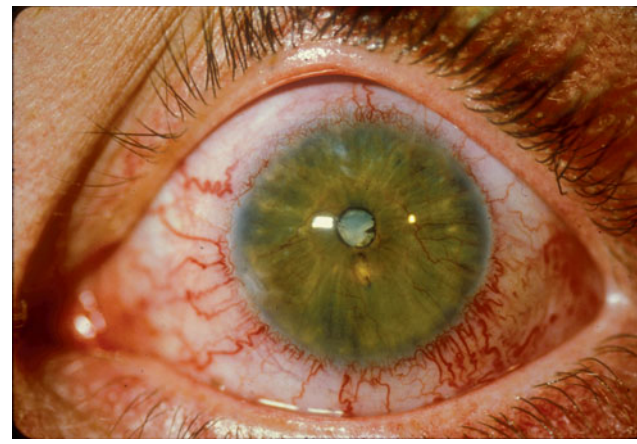

Fig. 46.2 Hemangioma of the conjunctiva. Photo courtesy of Jonathan Dutton

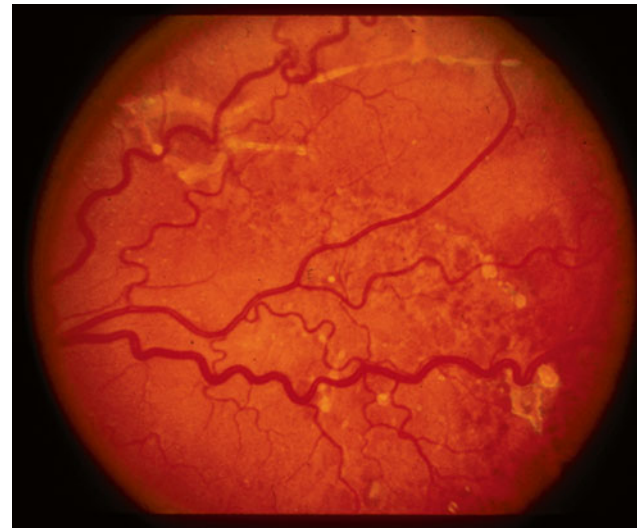

Fig. 46.3 Tortuous retinal vessels. Photo courtesy of Jonathan Dutton

with compact trabecular meshwork, amorphous material in the intertrabecular spaces, hyalinized trabecular meshwork, thickened trabecular beams, and degenerative changes in the elastic tissue.

Elevated episcleral venous pressure is also present in SWS [2, 11]. In separate studies, Weiss and Phelps found elevated episcleral venous pressure from arteriovenous fistulas in SWS patients. Phelps hypothesized that the extent of episcleral hemangiomas correlates with the severity of glaucoma. Aside from angle abnormalities and elevated episcleral venous pressure, glaucoma can also develop in the setting of retinal detachment with forward displacement of the iris and secondary angle-closure from peripheral anterior synechiae or neovascularization [6, 8].

Summary for the Clinician

- SWS is characterized by intracranial and facial angiomas, hemangiomas of the lid, episclera, conjunctiva, iris, ciliary body, or choroid.
- Glaucoma occurs in 30–70 % of individuals with SWS and patients with upper eyelid involvement are more likely to develop glaucoma. Of those that develop glaucoma, 60 % develop it before 2 years of age.
- Glaucoma may develop in SWS because of anterior chamber angle anomalies or elevated episcleral venous pressure.

46.2 Is Management of Glaucoma in SWS Different from the Typical Management of Primary Open Angle Glaucoma?

Since SWS is relatively uncommon, there are no large, long-term studies regarding the optimal management of glaucoma in this population. However there are several smaller studies and case reports that provide insight regarding the treatment of these individuals.

46.2.1 Medical Treatment of Glaucoma in SWS

The main difference in managing glaucoma in SWS compared to primary open-angle glaucoma (POAG) is that the glaucoma is less responsive to medical therapy [16]. Of the topical therapies

available, aqueous suppressants and miotics tend to be the most successful. A few studies regarding the use of latanoprost in these patients have shown that there is a higher nonresponse rate, especially in patients with early-onset glaucoma. However there are reports where patients with late-onset glaucoma had a robust response to latanoprost [4, 18].

46.2.2 Surgical Treatment of Glaucoma in SWS (Angle Surgery and Trabeculectomy)

When the onset of glaucoma is early, angle abnormalities are thought to be the source of elevated intraocular pressure (IOP). Since medical therapy is usually unsuccessful, goniotomy or trabeculotomy is typically the first line of therapy because these procedures target the anatomical abnormality. However these surgical approaches are typically less effective in SWS glaucoma than in primary congenital glaucoma [12]. When ineffective, the patient may require filtering surgery to control IOP. In general, standard trabeculectomy without antimetabolites has limited success in children, probably because of the rapid healing response and thick Tenon's layer.

Iwach et al. reviewed their medical and surgical management of glaucoma in 36 eyes of 30 patients with SWS [10]. They evaluated efficacy of interventions based on the length of time to subsequent medical or surgical intervention. In other words, a long time interval to subsequent intervention means better efficacy. Median stable intervals (length of time without increase in IOP or change in optic nerve) were 12 months with goniotomy, 21 months with trabeculotomy, 34 months with trabeculectomy, 25 months with argon laser trabeculoplasty, and 57 months with medications. They recommend goniotomy or trabeculotomy over trabeculectomy which was complicated by choroidal effusions in 24 % of patients. A posterior sclerotomy prior to entering the eye in filtration surgery has been recommended by some investigators to minimize the risk of serous choroidals and hypotony, while others recommend tight suturing of the flap instead [2]. However, since there are no large, prospective, randomized trials examining the use of posterior sclerotomies, their need remains debatable.

In juvenile or later-onset glaucoma, topical medications are typically the first-line of therapy but they frequently fail. Argon laser trabeculoplasty has been used to treat glaucoma in SWS but appears to have limited success [10]. The next line of therapy in these individuals is trabeculectomy. Ali et al. reported results in 7 eyes of 6 patients with SWS treated with trabeculectomy without antimetabolite who were followed for at least 9 months. Postoperatively, two eyes had adequate IOP control without the use of medications, four eyes required additional medication, and one eye required three additional trabeculectomies and postoperative medications to achieve control [3].

Antimetabolite-augmented trabeculectomy has been used in pediatric patients and a few case reports have shown them to be successful in refractory congenital glaucoma [13]. However, in patients with SWS less success has been reported [17]. The long-term effects of antimetabolite use in children must be considered given their longevity and potentially poor hygiene that can increase the risk of blebitis.

Alternatively, two centers in India have reported success in SWS patients using primary combined trabeculotomy–trabeculectomy for early-onset glaucoma without the placement of prophylactic sclerotomies [1, 12]. One study of 10 eyes of 9 patients showed IOP reductions from 28 to 11.8 mmHg, and all eyes maintained a postoperative IOP less than 16 mmHg without medications over a mean follow-up of 28 months [12]. Another study of 18 eyes reported IOP $\leq$ 22 mmHg in 11 eyes after a mean follow-up of 42 months with or without medications [1]. One benefit of these combined glaucoma procedures is that the surgery targets both mechanisms of SWS glaucoma, namely the angle abnormality (via trabeculotomy) and elevated episcleral venous pressure (via trabeculectomy). It also appears to be safe. Mandal used intravenous mannitol 1 h before surgery to lower IOP intraoperatively to minimize a sudden surgical drop in pressure and choroidal effusions [12].

46.2.3 Glaucoma Drainage Devices in SWS Glaucoma

Glaucoma drainage devices have been shown to be helpful in the management of glaucoma in SWS. In a study of 11 eyes of 10 patients with SWS glaucoma that underwent Ahmed valve placement, the cumulative probability of success was 79 % at 24 months, 59 % at 42 months, and 30 % at 60 months, comparable to the results of tube shunts in other types of glaucoma [9]. Success was defined as IOP less than 21 mmHg, without additional glaucoma surgery, expulsive choroidal hemorrhage, or retinal detachment. Treatment failed in four eyes with implant extrusion in one eye and IOP greater than 21 mmHg in three eyes at the last follow-up.

Budenz et al. used a two-staged implantation of the Baerveldt glaucoma implant (BGI) in patients with glaucoma in SWS. This technique was used in an attempt to reduce the potential complications of choroidal effusion and hemorrhage and to improve long-term IOP control. Allowing encapsulation around the plate before inserting the tube is thought to minimize hypotony when the tube becomes functional. However, they also used posterior sclerotomies at the time of surgery, prior to entering the eye. They report that all ten eyes of nine children had adequate IOP control (≤21 mmHg) and none needed additional glaucoma surgery during a 3-year follow-up. There were a few minor complications including two eyes with transient serous choroidal effusions, but they did not result in permanent visual loss. No intraoperative or postoperative suprachoroidal hemorrhages occurred. The authors conclude that two-stage BGI surgery appears to be a safe and effective treatment for refractory glaucoma in children with SWS [5].

46.2.4 Cyclodestruction in SWS Glaucoma

As it is in the treatment of many cases of glaucomas, one of the last procedures in management of glaucoma in SWS for patients who have failed other medical and surgical interventions is ablation of the ciliary body. In one study, cryocoagulation of the ciliary body resulted in a mean postoperative IOP of <22 mmHg in 6 of 7 patients after a mean follow-up of 4–5 years [16] (see Fig. 46.4). The risks of this procedure—including phthisis—limit its use in the early management of glaucoma or when visual acuity is good.

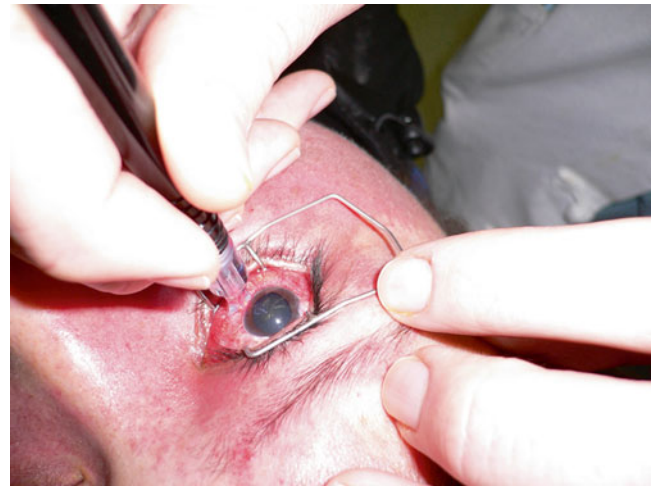

Fig. 46.4 Cyclophotocoagulation for refractory glaucoma in a patient with SWS. Photo courtesy of JoAnn A. Giaconi

46.2.5 Nonpenetrating Surgery in SWS Glaucoma

Recently, nonpenetrating glaucoma surgery has gained popularity. Because choroidal effusions following fistulizing surgery can occur in patients with SWS, nonpenetrating glaucoma surgery may offer a theoretical advantage; since there is no penetration of the anterior chamber during surgery, sudden intraoperative and postoperative hypotony may be avoided. A single case study of nonpenetrating deep sclerectomy reported reduction of IOP from 30 to 15 mmHg 6 months postoperatively. No intraoperative or postoperative complications occurred [14]. Further study is needed regarding the use of nonpenetrating techniques for this population.

Summary for the Clinician

- There are no large, long-term studies that dictate the optimal management of glaucoma in patients with SWS.
- SWS-associated glaucoma can be more difficult to control than other forms of glaucoma and there is a higher risk of surgical complications.
- Glaucoma in SWS is less responsive to medical therapy. Aqueous suppressants and miotics work best.
- Early-onset glaucoma in SWS is caused by angle abnormalities. Goniotomy or trabeculotomy is typically the first line of therapy in these cases but these procedures are usually less successful than in primary congenital glaucoma.
- For juvenile or later-onset glaucoma, topical medications are typically the first line of therapy but they frequently fail. The next step in treatment is usually a trabeculectomy or glaucoma drainage device.
- Nonpenetrating surgery has not been well-studied for glaucoma in SWS patients, though there may be theoretical advantages to this approach.

46.3 What Problems Should Be Anticipated in the Management of SWS Glaucoma?

In individuals with SWS and glaucoma, there is a higher nonresponse rate to medical therapy, especially if the glaucoma onset is early. Thus surgical therapy is often needed to lower the IOPs to a target range.

The main concern when managing glaucoma in SWS is related to intraoperative and postoperative complications. Several early publications reported complications of incisional surgery in these patients, including expulsive choroidal hemorrhages and sudden intraoperative choroidal effusions. These complications are thought to be related to elevated episcleral venous pressure. Aiming for a higher target, IOP may reduce the risk of these complications. Expulsive choroidal hemorrhages may also be related to fragile choroidal vascular walls. Several precautions have been proposed to reduce the risk of these complications; they include reducing IOP immediately prior to surgery with hyperosmotic agents or treating the choroidal hemangioma with radiotherapy prior to intraocular surgery.

Choroidal effusions have also been reported with intraocular surgery and may be secondary to a rapid shift of fluid from choroidal capillaries to the suprachoroidal space in the face of a sudden IOP drop and elevated episcleral and choroidal venous pressure. Development of a choroidal effusion intraoperatively is signaled by sudden shallowing of the anterior chamber. If this occurs, drainage may be indicated. If surgery is then planned for the second eye of a patient who has developed intraoperative choroidal effusions in the first eye, placement of a prophylactic sclerotomy may be indicated.

Others recommend the regular placement of posterior sclerotomies prior to entry into the eye of an SWS patient to reduce these risks, especially if the eye has extensive choroidal hemangiomas. Sclerotomies allow suprachoroidal effusions to drain out of the eye as they form. However a study reviewing 34 glaucoma filtering surgeries without

posterior sclerotomy on 17 patients showed no intraoperative choroidal effusions, detachments, or hemorrhages. Postoperatively, choroidal effusions occurred in six individuals but all were transient [7].

Another way to decrease the risk of choroidal effusion is to limit intraoperative hypotony and thereby reduce the amount of time for expansion of the vascular compartment. This goal can be achieved by reducing the time the eye is open to atmospheric pressure through quick suturing of the scleral flap. This may be facilitated by preplacing scleral flap sutures prior to creating the trabeculectomy opening. Tightly suturing the scleral flap may also be helpful in the postoperative period.

Summary for the Clinician

- Glaucoma in SWS may be less responsive to medical therapy.
- Intraoperative and postoperative complications are more common in patients with SWS.
- Expulsive choroidal hemorrhages and sudden intraoperative choroidal effusions have been reported. Choroidal effusions may be secondary to a rapid shift of fluid from choroidal capillaries to the suprachoroidal space in the face of elevated episcleral and choroidal venous pressure when the IOP is suddenly lowered.
- Placement of prophylactic posterior sclerotomies is debated.
- Surgical risks may be reduced by lowering preoperative IOP with hyperosmotic agents, treating the choroidal hemangioma with radiotherapy prior to intraocular surgery, reducing the time the eye is open to atmospheric pressure by quickly and tightly sewing the scleral flap closed during trabeculectomy.

46.4 What Kind of Outcomes Can Be Expected in this Type of Glaucoma?

While there are no large long-term studies regarding the visual outcomes of patients with glaucoma in the setting of SWS, it is thought that the severity of glaucoma is greater in SWS compared to POAG. However there are several small studies with short follow-ups that report similar outcomes to POAG. Iwach et al. found that 23 of 35 eyes had IOP less than 25 mmHg and 13 eyes had visual acuity better than 20/40 at their last follow-up [10]. Budenz et al. reported that eyes with BGIs had IOP less than or equal to 21 mmHg and needed no further glaucoma surgery at 3 years postoperatively [5]. Mean IOP was approximately 17 mmHg and final vision ranged from 20/20 to 20/30 in 8 of 10 eyes.

Summary for the Clinician

- SWS eyes are believed to have more severe glaucoma than POAG eyes.
- Several small studies with relatively short follow-ups have reported eyes to have good outcomes with vision in the 20/40 or better range.

References

1. Agarwal HC, Sandramouli S, Sihota R, Sood N. Sturge-Weber syndrome: management of glaucoma with combined trabeculotomy-trabeculectomy. Ophthalmic Surg. 1993;24:399–402.
2. Albert DM, Jakobiec FA. Principles and practice of ophthalmology. 2nd ed. Philadelphia: W.B. Saunders; 2000.
3. Ali MA, Fahmy IA, Spaeth GL. Trabeculectomy for glaucoma associated with Sturge-Weber syndrome. Ophthalmic Surg. 1990;21:352–5.
4. Anand R. Photodynamic therapy for diffuse choroidal hemangioma associated with Sturge Weber syndrome. Am J Ophthalmol. 2003;136:758–60.
5. Budenz DL, Sakamoto D, Eliezer R, et al. Two-staged Baerveldt glaucoma implant for childhood glaucoma

associated with Sturge-Weber syndrome. Ophthalmology. 2000;107:2105–10.
6. Cibis GW, Tripathi RC, et al. Glaucoma in Sturge-Weber syndrome. Ophthalmology. 1984;91:1061–71.
7. Eibschitz-Tsimhoni M, Lichter PR, Del Monte MA, et al. Assessing the need for posterior sclerotomy at the time of filtering surgery in patients with Sturge-Weber syndrome. Ophthalmology. 2003;110: 1361–3.
8. Font RL, Ferry AP. The phakomatoses. Int Ophthalmol Clin. 1972;12:1.
9. Hamush NG, Coleman AL, Wilson MR. Ahmed glaucoma valve implant for management of glaucoma in Sturge-Weber syndrome. Am J Ophthalmol. 1999;128:758–60.
10. Iwach AG, Hoskins HD, Hetherington J, et al. Analysis of surgical and medical management of glaucoma in Sturge-Weber syndrome. Ophthalmology. 1990;97:904–9.
11. Kranemann CF, Pavlin CJ, Trope GE. Ultrasound biomicroscopy in Sturge-Weber-associated glaucoma. Am J Ophthalmol. 1998;125:119–21.
12. Mandal AK. Primary combined trabeculotomy-trabeculectomy for early-onset glaucoma in Sturge-Weber syndrome. Ophthalmology. 1999;106: 1621–7.
13. Mandal AK, Walton DS, John T, et al. Mitomycin C-augmented trabeculectomy in refractory congenital glaucoma. Ophthalmology. 1997;104:996–1001, discussion 1002–3.
14. Rebolleda G. Nonpenetrating deep sclerectomy for Sturge-Weber syndrome. Ophthalmology. 2001;108: 2152–3.
15. Sullivan TJ, Clarke MP, Morin JD. The ocular manifestations of the Sturge-Weber syndrome. J Pediatr Ophthalmol Strabismus. 1992;29:349–56.
16. van Emelen C, et al. Treatment of glaucoma in children with Sturge-Weber syndrome. J Pediatr Ophthalmol Strabismus. 2000;37:29–34.
17. Walton DS. Discussion: analysis of surgical and medical management of glaucoma in Struger–Weber syndrome. Ophthalmology. 1990;97:909 [Comment on: Ophthalmology 1990;97:904–9].
18. Yang CB, Freedman SF, Myers JS, et al. Use of latanoprost in the treatment of glaucoma associated with Sturge-Weber syndrome. Am J Ophthalmol. 1998;126:600–2.

Glaucomas: Glaucoma and the Cornea

47

JoAnn A. Giaconi

Core Messages

- Intraocular pressure measurements are affected by corneal hydration.
- Corneal edema can result from high intraocular pressure, topical medications, laser and incisional glaucoma surgery.
- Corneas with tenuous endothelial function and density are most at risk for decompensation following interventions for glaucoma.
- Certain corneal diseases can lead to glaucoma.

47.1 How Does IOP Affect the Cornea?

From the glaucoma specialist's standpoint, the cornea has generated a great deal of interest since the Ocular Hypertension Treatment Study (OHTS) highlighted the importance of central corneal thickness as a risk factor for glaucoma development. The cornea has always been important though, because a compact and transparent cornea is necessary for a clear view of the optic nerve, for good visual acuity to perform visual fields, and for accurate measurements of intraocular pressure [1, 2]. The effects of glaucoma and glaucoma treatment on the corneal endothelium are of particular concern, as a compromised endothelium poses a great risk for corneal decompensation.

The cornea is a sandwich of perfectly hydrated stroma in between the epithelium and the endothelium, which both guard against excessive hydration. The stroma makes up over 90 % of the cornea's structure and has a natural tendency to swell due to its content of glycosoaminoglycans and protein that draw fluid into it [3]. Anteriorly, tight junctions between epithelial cells prevent the tears from entering the stroma. Posteriorly, endothelial cell layer leaky junctions allow aqueous humor to seep into the stroma to provide nutrition, but simultaneously these cells are actively drawing fluid out via an active pump mechanism. Additionally, IOP produces an outward compressive force that helps keep the stromal layers compact. In part, corneas become edematous during hypotony because this compressive effect of IOP is lost. On the other hand, in cases of acutely elevated IOP, microcystic epithelial edema results when high IOP drives fluid across the loose endothelial junctions.

The relationship between IOP and corneal endothelial cell loss is not fully understood. In acute

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angle-closure attacks with very high IOP, the average loss of endothelial cells is 23–35.1 %, with reported losses as high as 68 %. Cell loss correlates with the *duration* of IOP elevation in acute angle-closure, with significant losses beginning at 72 h duration [4–6]. With chronic and moderately elevated IOP, what happens to the endothelium is less clear. In an elegant study in which ocular hypertension was induced by laser in one eye of subject monkeys, endothelial cell density (ECD) was lower in the hypertensive eye (33 % loss) compared to the control eye after 2.5 years. Average IOP was double that seen in the control eyes (ranging from 25 to 59 mmHg). The ECD decrease correlated with duration of IOP elevation but not to the height of IOP elevation [7]. In two clinical studies, ECD was measured in glaucoma patients and cataract control patients. ECD was lower in glaucoma patients vs. controls, lower in primary angle-closure glaucoma vs. primary open-angle glaucoma, and lower in those patients on 3–4 topical medications vs. those on 1–2 medications. The ECD count correlated with IOP level; however, if the few patients with extremely low ECD (i.e., those status post acute angle-closure attacks) were removed from the analysis, the correlation was no longer significant [8, 9].

With the common clinical scenario of chronic open-angle glaucoma and IOP in the mid to high 20s range, there may be some statistically significant loss of endothelial cells, but it does not appear to be clinically significant. In cases of acute angle-closure glaucoma lasting 72 h or more, very high losses of ECD may be sustained that can prove clinically significant, particularly in eyes that go on to have further endothelial cell insults such as intraocular surgery.

Summary for the Clinician

- IOP compresses the corneal stroma to help keep it compact; with hypotony this compressive effect is lost, contributing to corneal swelling.
- Acute angle-closure attacks with very high IOP lasting ≥72 h can lead to large losses of endothelial cells.
- Chronically elevated IOP at moderate levels may lead to a decrease in ECD, but this does not appear to be clinically significant for most patients.

47.2 What Effect Do Topical Medications Have on the Corneal Endothelium?

Endothelial toxicity is always feared with application of a new compound to the eye. Multiple clinical trials have shown that there is no clinically significant decline in ECD with the use of different topical glaucoma medications. The longest follow-up published shows no effect over a 6-year period [10–12]. Carbonic anhydrase inhibitors (CAI) specifically raised concerns, given a number of reports that showed corneal decompensation and increased central corneal thickness after topical CAI use [13–17]. Carbonic anhydrase (CA) isoenzymes are found in the ciliary epithelium and corneal endothelium. The isoenzyme CA II plays a major role in keeping the cornea in a relatively steady state of dehydration [18]. If CA II is inhibited, and dorzolamide is a major inhibitor, the cornea may swell and lose transparency. As it turns out, CAIs mainly pose a risk of decompensation in corneas with borderline endothelial function/density. In healthy corneas, these medications can be used safely [10, 12].

Summary for the Clinician

- Carbonic anhydrase is found in the cornea.
- Topical CAIs have caused corneal decompensation in eyes with poor endothelial function.

47.3 What Effect Do Topical Medications Have on the Corneal Epithelium?

Preservatives are necessary to prevent microbial contamination of liquid medication, but they can have inflammatory, toxic, and allergic side effects. Benzalkonium chloride (BAK) is the single most commonly used ocular preservative today. In vitro studies on immortalized human cornea cells show that medication with BAK has a significant kill effect on these cells compared to non-BAK medication [19]. Studies on rabbits show that BAK causes desquamation of superficial epithelial layers [20]. These effects are thought to affect the tolerability of topical drops. Two large European studies examined ocular signs and symptoms in thousands of patients using preserved and nonpreserved glaucoma medications. They found that the use of nonpreserved drops was associated with about half as many complaints of dry eye symptoms, pain on instillation, foreign body sensation and burning, as well as fewer objective ocular signs than the use of preserved drops [21, 22]. Other preservatives found in commercially available glaucoma medications include benzododecinium bromide, Purite (a stabilized oxychloro complex), and SofZia, a proprietary ionic buffer system that upon contact with the eye falls apart into nontoxic component parts (boric acid, propylene glycol, sorbitol, and zinc chloride). BAK and other older preservatives have been found to enhance ocular penetration of IOP-lowering medications by disrupting epithelial permeability [23]. A concern with formulations using BAK alternatives is whether they will penetrate the ocular surface sufficiently and have equal efficacy to the original formulations—something manufacturers have had to demonstrate for approval in the US market. Preservatives also may have negative toxic and inflammatory effects on the conjunctiva, which theoretically may affect the future success of filtering surgery [24–26]. Increased expression of inflammatory markers and decreased mucin production with the use of BAK has been reported [21].

Another possible side effect of topical medications is subclinical neurotrophic keratopathy [10, 28]. The cornea is a highly innervated tissue. This innervation serves multiple purposes in the cornea's defense. It is responsible for the aversion response, trophic effects that maintain a normally functioning cornea, and the neural feedback loop that is important in regulating the tear film [27]. A study published in 2006 examined the effects of chronic topical glaucoma medication use in a small cohort of 26 OHTS patients. Using confocal microscopy, the authors of this study found the sub-basal nerve plexus was decreased in patients taking chronic topical therapy compared to those in the observation group, and they questioned whether topical medications were causing a subclinical neurotrophic keratitis [10]. If this study can be replicated this may be an important finding. Decreased sensation, as seen in penetrating keratoplasty patients where corneal nerves are severed, can lead to epithelial dysfunction via increased permeability, decreased cell migration, and decreased cell mitosis [27]. This may explain surface changes often seen with chronic topical medication use, such as tear film disturbances and punctate epithelial erosions (Fig. 47.1).

Summary for the Clinician

- Benzalkonium chloride is the most common ocular preservative and is toxic to corneal epithelium, which can lead to ocular surface signs and symptoms.
- Chronic topical medication use may possibly affect corneal innervation, which may explain ocular surface side effects.

47.4 What Effect Does Laser Glaucoma Surgery Have on the Cornea?

Laser iridotomy and trabeculoplasty are generally considered to be treatment options with a relatively low risk of adverse effects in comparison to incisional surgery. Reports of corneal decompensation after variable amounts of

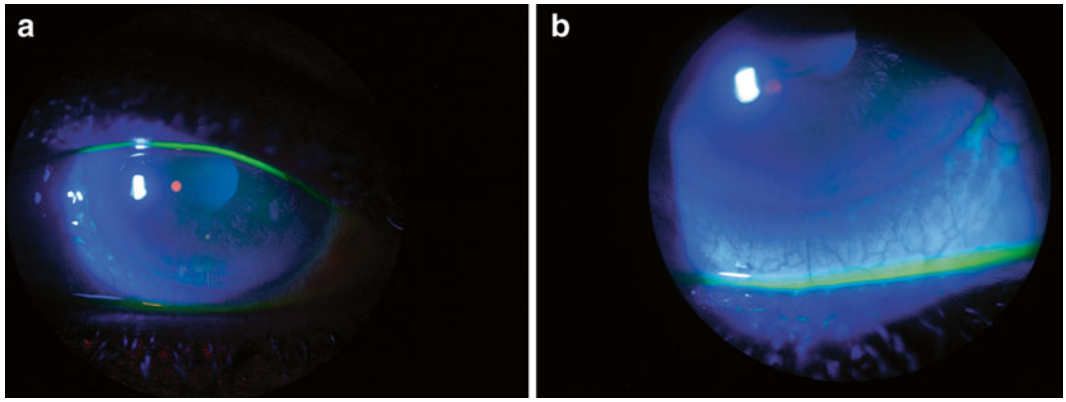

Fig. 47.1 Pair of eyes where only one eye received topical glaucoma medications. The eye receiving topical glaucoma medications exhibits inferior punctate epithelial erosions (**a**). The fellow eye had a healthy ocular surface (**b**)

elapsed time (immediate to 16 years later) have been reported following laser iridotomy, particularly argon iridotomy [28–32]. A report from Japan cites 39 eyes that developed argon laser iridotomy-induced bullous keratopathy requiring penetrating keratoplasty [33]. Over half the eyes (59 %) had received a prophylactic iridotomy without ever having suffered an acute angle-closure attack (remember that acute angle-closure can dramatically decrease the baseline endothelial cell count—see Sect. 47.1). Of note, nearly a quarter of patients in this report had preexisting corneal guttata, and no history of other intraocular procedures was reported. A case series from Singapore similarly describes 14 eyes with inferior corneal edema leading to generalized decompensation following peripheral laser iridotomy [34]. It must be noted that these alarming cases represent a rare long-term complication. The authors estimated that these 14 eyes comprised 0.33 % of all laser iridotomies performed over the 12-year review period.

It has been hypothesized that aqueous humor dynamics are altered by an iridotomy. Using a rabbit model, it has been shown that upon pupillary constriction a jet of aqueous fluid is forced through an iridotomy and is directed toward the endothelium. This jet of fluid may mechanically damage the endothelium [35]. In a human study using specular microscopy, Nd:YAG laser was shown to induce corneal endothelial damage in nearly all iridotomies, although damage was usually confined to the immediate area of laser treatment. Differences in surface area damaged may be due to differences in the iris/cornea distance and laser energy used [36].

With selective laser trabeculoplasty (SLT) no significant damage to the corneal endothelium has been found [37, 38] in most instances. One study found transient dark spots on specular microscopy after treatment, with more spots in compromised corneas and those with darkly pigmented deposits [39]. There are rare case reports of acute corneal edema following SLT associated with subsequent corneal thinning and hyperopic shift [40]. The cause of this corneal edema and subsequent changes is unknown.

Summary for the Clinician

- Laser iridotomy can cause localized loss of endothelial cells. There are reports of delayed corneal decompensation following argon laser iridotomy, although they are rare.
- Laser trabeculoplasty has been associated with very rare cases of corneal edema.

47.5 What Effect Does Incisional Glaucoma Surgery Have on the Cornea?

The most devastating effect to the cornea of incisional glaucoma surgery is a flat chamber postoperatively. If the lens touches the central cornea over 50 % of the endothelial cells can be lost. In shallow chambers where only the peripheral cornea is in contact with the iris, ECD decreases have been reported to be 8.1 ± 15.4 %. In cases where there is no chamber shallowing, average losses after surgery are 1.6 ± 19.1 % [41, 42]. To keep everything in perspective, average ECD losses after phacoemulsification are reported to be 8–10 % at 1 year [43, 44].

47.5.1 Antimetabolite Use and the Cornea

The use of adjunctive antimetabolite with trabeculectomy has been examined as a possible source of corneal toxicity. Mitomycin-C is generally considered safe to the cornea in its current clinical uses—for example, LASIK surgeons apply it directly to the stroma in doses of 0.02 % to prevent corneal haze and no clinical reports of damage to the endothelium in normal human corneas have been reported to date [45]. However, directly applied to endothelial cells there is a dose-dependent toxic effect [46]. 5-Fluorouracil is especially toxic to epithelium, as it inhibits cells with rapid turnover. Punctate epitheliopathy and epithelial defects have been reported. Subtle changes in the endothelium seen on confocal microscopy are also reported [47]. Studies of both antimetabolites have measured low concentrations in the aqueous humor after external application [48, 49]. Given that these agents are capable of subclinical toxicity within the anterior chamber at currently used concentrations, theoretically, there may be a risk of decompensation in eyes with unhealthy endothelium at baseline. There do exist case reports of corneal decompensation after mitomycin-C trabeculectomy in patients with corneal guttata [50].

47.5.2 Glaucoma Drainage Devices and the Cornea

There is a significant body of literature on tube shunts and corneal decompensation, although most of this literature concentrates on corneal grafts. Corneal grafts with glaucoma drainage devices in place have a survival rate as low as 25.8 % at 2 years [51]. Corneal grafts are more tenuous to begin with than a normal cornea, as many grafts have a high rate of endothelial cell loss in the first 5 postoperative years [52]. In the past, tube shunts were reserved for eyes with refractory glaucomas whose corneas may have already withstood many intraocular insults, placing them in a precarious situation. Very few published studies exist that prospectively measure endothelial cell counts after tube shunt implantation. In one study measuring endothelial cell counts following Molteno implantation for aphakic and pseudophakic glaucoma, endothelial cell loss was 2 cells/mm^2 per month [53], whereas normal aging estimates a loss of 1.3 cells/mm^2 per month [54].

The decompensation rate of native corneas following tube shunts has not been studied as greatly, but there are a few prospective studies that provide data. The 5-year outcome results from the multicenter, randomized controlled Trabeculectomy versus Tube (TVT) study reported a 16 % rate of corneal edema after Baerveldt tube shunt versus 9 % after trabeculectomy [55]. The Ahmed Baerveldt Comparison (ABC) study 3-year outcomes publication reported rates of corneal edema not attributable to previous corneal disease at 6.4 % after Ahmed valves and 10.1 % after Baerveldt shunts [56]. In both the ABC and the Ahmed versus Baerveldt (AVB) [57] studies the rates of corneal decompensation were higher (2–3 times higher) in the Baerveldt groups than in the Ahmed groups. Baseline endothelial cell counts have not been reported from these studies, but it is surmised that many eyes receiving tube shunts may have lower baseline endothelial cell counts due to a greater number of previous intraocular surgeries that may have damaged endothelium [58]. There is

also evidence that aqueous humor composition may be different in eyes with glaucoma. In a study analyzing aqueous humor from eyes with tube shunts, there were elevated levels of proteins known to play a role in oxidative stress, apoptosis, inflammation, and immunity [59].

Summary for the Clinician

- A flat chamber with cornea-lens touch can devastate the corneal endothelium.
- Mitomycin-C is considered safe for the cornea in commonly used external concentrations.
- 5-Fluorouracil is toxic to corneal epithelium.
- Both antimetabolites have been found in aqueous humor after external application. In eyes with compromised endothelium this may be problematic.
- Tube shunts are associated with a high rate of corneal graft decompensation.
- Tube shunts are associated with a clinically significant rate of native corneal decompensation.

47.6 How Do Corneal Diseases Affect Glaucoma?

Corneal diseases can cause secondary glaucoma, both of the open and closed angle type. Ocular herpes simplex virus may be associated with early or late IOP elevations. Initially, it presents with elevated intraocular pressure due to a trabeculitis and physical blockade of the trabecular meshwork by cells, fibrin and plasma proteins [60], or later with glaucoma induced by steroid treatment. In a retrospective review of HSV, the following signs were found to be associated with ocular hypertension: disciform keratouveitis (44 %), stromal keratouveitis (36 %), disciform keratitis (10 %), stromal keratitis (4 %), scleral keratitis/limbitis (2 %), and metaherpetic ulcer (4 %) [61].

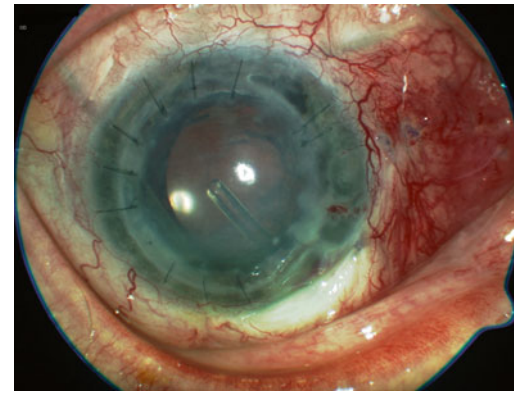

Fig. 47.2 Patient with ICE syndrome status post multiple penetrating keratoplasties and glaucoma surgeries due to overgrowth of abnormal endothelium over the angle causing peripheral anterior synechiae. Notice tube shunt in each quadrant

Bacterial and fungal keratitis can lead to glaucoma through inflammatory changes leading to peripheral synechiae formation, pupillary block, and even malignant glaucoma [62]. In iridocorneal endothelial (ICE) syndrome, abnormal endothelium can grow over the angle and cause secondary angle-closure glaucoma. Glaucoma in ICE syndrome can be difficult to control and multiple procedures are often necessary (Fig. 47.2). Tube shunts have better survival than trabeculectomies because the abnormal endothelium can grow over the trabeculectomy ostium and cut off filtration [63], whereas tubes rarely become occluded. Some have suggested creating an iridectomy under the intracameral portion of the tube to prevent synechial formation around the tube.

Summary for the Clinician

- Herpes simplex, bacterial/fungal keratitis, and ICE syndrome are corneal diseases that frequently lead to secondary glaucoma.

References

1. Damji KF, Muni RH, Munger RM. Influence of corneal variables on accuracy of intraocular pressure measurement. J Glaucoma. 2003;12:69–80.
2. Whitacre MM, Stein R. Sources of error with use of Goldmann-type tonometers. Surv Ophthalmol. 1993;38:1–30.
3. Nishida T. Basic science: cornea, sclera, and ocular adnexa anatomy, biochemistry, physiology, and biomechanics. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea: fundamentals of cornea and external disease. St. Louis: Mosby; 1997. p. 3–27.
4. Bigar F, Witmer R. Corneal endothelial changes in primary acute angle-closure glaucoma. Ophthalmology. 1982;89:596–9.
5. Setälä K. Corneal endothelial cell density after an attack of acute glaucoma. Acta Ophthalmol (Copenh). 1979;57:1004–13.
6. Sihota R, Lakshmaiah NC, Titiyal JS, et al. Corneal endothelial status in the subtypes of primary angle-closure glaucoma. Clin Exp Ophthalmol. 2003;31:492–5.
7. Ollivier FJ, Brooks DE, Komaromy AM, et al. Corneal thickness and endothelial cell density measured by non-contact specular microscopy and pachymetry in *Rhesus macaques* (*Macaca mulatta*) with laser-induced ocular hypertension. Exp Eye Res. 2003;76:671–7.
8. Gagnon MM, Boisjoly HM, Brunette I, et al. Corneal endothelial cell density in glaucoma. Cornea. 1997;16:314–8.
9. Zarnowski T, Lekawa A, Dyduch A, et al. Corneal endothelial density in glaucoma patients. Klin Oczna. 2005;107:448–51.
10. Baratz KH, Nau CB, Winter EJ, et al. Effects of glaucoma medications on corneal endothelium, keratocytes, and subbasal nerves among participants in the Ocular Hypertension Treatment Study. Cornea. 2006;25:1046–52.
11. Lass JH, Eriksson GL, Osterling L, et al. Comparison of the corneal effects of latanoprost, fixed combination latanoprost-timolol, and timolol: a double-masked, randomized, one-year study. Ophthalmology. 2001;108:264–71.
12. Lass JH, Khosrof SA, Laurence JK, et al. A double-masked, randomized, 1-year study comparing the corneal effects of dorzolamide, timolol, and betaxolol. Dorzolamide Corneal Effects Study Group. Arch Ophthalmol. 1998;116:1003–10.
13. Konowal A, Morrison JC, Brown SV, et al. Irreversible corneal decompensation in patients treated with topical dorzolamide. Am J Ophthalmol. 1999;127:403–6.
14. Wirtitisch MG, Findl O, Heinzl H, Drexler W. Effect of dorzolamide hydrocholoride on central corneal thickness in humans with cornea guttata. Arch Ophthalmol. 2007;125:1345–50.
15. Inoue K, Okugawa K, Oshika T, Amano S. Influence of dorzolamide on corneal endothelium. Jpn J Ophthalmol. 2003;47:129–33.
16. Giasson CJ, Nguyen TQ, Boisjoy HM, et al. Dorzolamide and corneal recovery from edema in patients with glaucoma or ocular hypertension. Am J Ophthalmol. 2000;129:144–50.
17. Kaminski S, Hommer A, Koyuncu D, et al. Influence of dorzolamide on corneal thickness, endothelial cell count and corneal sensibility. Acta Ophthalmol Scand. 1998;76:78–9.
18. Hull DS, Green K, Boyd M, Wynn HR. Corneal endothelium bicarbonate transport and the effect of carbonic anhydrase inhibitors on endothelial permeability and fluxes and corneal thickness. Invest Ophthalmol Vis Sci. 1977;16:883–92.
19. Yee RW, Norcom EG, Zhao XC. Comparison of the relative toxicity of travoprost 0.004% without benzalkonium chloride and latanoprost 0.005% in an immortalized human cornea epithelial cell culture system. Adv Ther. 2006;23:511–9.
20. Whitson JT, Cavanagh HD, Lakshman N, Petroll WM. Assessment of corneal epithelial integrity after acute exposure to ocular hypertensive agents preserved with and without benzalkonium chloride. Adv Ther. 2006;23:663–71.
21. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002;86:418–23.
22. Jaenen N, Baudouin C, Pouliquen P, et al. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol. 2007;17:341–9.
23. Ramselaar JA, Boot JP, van Haeringen NJ, et al. Corneal epithelial permeability after instillation of ophthalmic solutions containing local anaesthetics and preservatives. Curr Eye Res. 1988;7:947–50.
24. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. Arch Ophthalmol. 1994;112:1437–45.
25. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. II. The outcome of filtration surgery. Arch Ophthalmol. 1994;112:1446–54.
26. Broadway DC, Grierson I, Stürmer J, Hitchings RA. Reversal of topical antiglaucoma medication effects on the conjunctiva. Arch Ophthalmol. 1996;114:262–7.
27. Darwish T, Brahma A, Efron N, O'Donnell C. Subbasal nerve regeneration after penetrating keratoplasty. Cornea. 2007;26:935–40.
28. Martone G, Frezzotti P, Tosi GM, et al. An in vivo confocal microscopy analysis of effects of topical antiglaucoma therapy with preservative on corneal innervation and morphology. Am J Ophthalmol. 2009;147:725–35.
29. Schwartz AL, Martin NF, Weber PA. Corneal decompensation after argon laser iridotomy. Arch Ophthalmol. 1988;106:1572–4.

30. Jeng S, Lee JS, Huang SC. Corneal decompensation after argon laser iridectomy—a delayed complication. Ophthalmic Surg. 1991;22:565–9.
31. Zabel RW, Mac Donald IM, Mintsioulis G. Corneal endothelial decompensation after argon laser iridotomy. Can J Ophthalmol. 1991;26:367–73.
32. Wilhelmus KR. Corneal edema following argon laser iridotomy. Ophthalmic Surg. 1992;23:533–7.
33. Ang LP, Higashihara H, Sotozono C, et al. Argon laser iridotomy-induced bullous keratopathy a growing problem in Japan. Br J Ophthalmol. 2007;91: 1613–5.
34. Lim LS, Ho CL, Ang LP, et al. Inferior corneal decompensation following laser peripheral iridotomy in the superior iris. Am J Ophthalmol. 2006;142: 166–8.
35. Yamamoto Y, Uno T, Shisida K, et al. Demonstration of aqueous streaming through a laser iridotomy window against the corneal endothelium. Arch Ophthalmol. 2006;124:387–93.
36. Kerr Muir MG, Sherrard ES. Damage to the corneal endothelium during Nd/YAG photodisruption. Br J Ophthalmol. 1985;69:77–85.
37. Rouhiainen H, Kemppinen P. Corneal endothelial cell density after trabeculoplasty. Ophthalmologica. 1988; 196:182–4.
38. Lesiewska-Junk H, Malukiewicz-Wiśiewska G. Corneal endothelial cell density and corneal thickness after laser trabeculoplasty. Klin Oczna. 1999;101: 189–90.
39. Ong K, Ong L, Ong L. Corneal endothelial changes after selective laser trabeculoplasty. Clin Exp Ophthalmol. 2013;41:537–40.
40. Knickelbein JE, Singh H, Flowers BE, et al. Acute corneal edema with subsequent thinning and hyperopic shift following selective laser trabeculoplasty. J Cataract Refract Surg. 2014;40:1731–5.
41. Smith DL, Skuta GL, Lindenmuth KA, et al. The effect of glaucoma filtering surgery on corneal endothelial cell density. Ophthalmic Surg. 1991;22: 251–5.
42. Fiore PM, Richter CU, Arzeno G, et al. The effect of anterior chamber depth on endothelial cell count after filtration surgery. Arch Ophthalmol. 1989;107: 1609–11.
43. Werblin TP. Long-term endothelial cell loss following phacoemulsification: model for evaluating endothelial damage after intraocular surgery. Refract Corneal Surg. 1993;9:29–35.
44. Tingey DP, Nichols BD, Jung SE, Randall PE. Corneal endothelial response to polymethylmethacrylate versus hydrogel lenses after phacoemulsification. Can J Ophthalmol. 1991;26:3–6.
45. Song JS, Kim JH, Yang M, et al. Mitomycin-C concentration in cornea and aqueous humor and apoptosis in the stroma after topical mitomycin-C application: effects of mitomycin-C application time and concentration. Cornea. 2007;26:461–7.
46. Wu KY, Hong SJ, Huang HT, et al. Toxic effects of mitomycin-C on cultured corneal keratocytes and endothelial cells. J Ocul Pharmacol Ther. 1999;15:401–11.
47. Lattanzio FA, Sheppard JD, Allen RC, et al. Do injections of 5-fluorouracil after trabeculectomy have toxic effects on the anterior segment? J Ocul Pharmacol Ther. 2005;21:223–35.
48. Seah SK, Prata JA, Minckler DS, et al. Mitomycin-C concentration in human aqueous humour following trabeculectomy. Eye. 1993;7:652–5.
49. Kondo M, Araie M. Concentration change of fluorouracil in the external segment of the eye after subconjunctival injection. Arch Ophthalmol. 1988;106: 1718–21.
50. Fukuchi T, Hayakawa Y, Hara H, Abe H. Corneal endothelial damage after trabeculectomy with mitomycin C in two patients with glaucoma with corneal guttata. Cornea. 2002;21:300–4.
51. Alvarenga LS, Mannis MJ, Brandt JD, et al. The long-term results of keratoplasty in eyes with a glaucoma drainage device. Am J Ophthalmol. 2004;138:200–5.
52. Bourne WM, McLaren JW. Clinical responses of the corneal endothelium. Exp Eye Res. 2004;78:561–72.
53. McDermott ML, Swendris RP, Shin DH, et al. Corneal endothelial cell counts after Molteno implantation. Am J Ophthalmol. 1993;115:93–6.
54. Yee RW, Matsuda M, Schultz RO, Edelhauser HF. Changes in the normal corneal endothelial cellular pattern as a function of age. Curr Eye Res. 1985; 4:671–8.
55. Gedde SJ, Herndon LW, Brandt JD, et al. Postoperative complications in the Trabeculectomy versus Tube (TVT) study during 5 years of follow up. Am J Ophthalmol. 2012;153:804–14.
56. Barton K, Feuer WJ, Budenz DL, et al. Three-year treatment outcomes in the Ahmed Baerveldt Comparison study. Ophthalmology. 2014;121:1547–57.
57. Christakis PG, Tsai JC, Kalenak JW, et al. The Ahmed versus Baerveldt study: three-year treatment outcomes. Ophthalmology. 2013;120:2232–40.
58. Zalloum JN, Ahuja RM, Shin D, Weiss JS. Assessment of corneal decompensation in eyes having undergone Molteno shunt procedures compared to eyes having undergone trabeculectomy. CLAO J. 1999;25:57–60.
59. Anshu A, Price MO, Richardson MK, et al. Alterations in the aqueous humor proteome in patients with a glaucoma shunt device. Mol Vis. 2011;17:1891–900.
60. Jones III R, Pasquale LR, Pavan-Langston D. Herpes simplex virus: an important etiology for secondary glaucoma. Int Ophthalmol Clin. 2007;47:99–107.
61. Falcon MG, Williams HP. Kerato-uveitis and glaucoma. Trans Ophthalmol Soc U K. 1978;98:101–4.
62. Jain V, Maiti A, Shome D, et al. Aspergillus-induced malignant glaucoma. Cornea. 2007;26:762–3.
63. Doe EA, Budenz DL, Gedde SJ, Imami NK. Long-term surgical outcomes of patients with glaucoma secondary to the iridocorneal endothelial syndrome. Ophthalmology. 2001;108:1789–95.

Glaucomas: Uveitic Glaucoma

48

Lesya Shuba and Young H. Kwon

Core Messages

- Making a correct diagnosis of the etiology of intraocular inflammation is the first and most important step in the management of uveitic glaucoma.
- Glaucoma is seen in approximately 10 % of patients with uveitis.
- Glaucoma is more common with certain types of uveitis.
- Careful history and follow-up help distinguish steroid-induced IOP rise from uveitis-induced IOP rise.
- Uveitic glaucoma initially should be managed medically—to decrease inflammation and IOP. However, glaucoma medications can often have unpredictable effects on IOP in the setting of uveitis.
- Laser trabeculoplasty has no role in uveitic glaucoma, but may be tried in steroid-induced glaucoma.
- Glaucoma surgery should be considered in patients on maximum tolerated medical treatment when there is (1) significant optic nerve damage from chronic/intermittent IOP elevation or (2) significant elevation of IOP causing high risk of optic nerve damage, irrespective of the present degree of optic neuropathy.
- Inflammation must be controlled preoperatively for optimum outcomes.
- There is no significant difference in the outcomes between Baerveldt and Ahmed shunts in uveitic glaucoma.

48.1 How Often Does One See Glaucoma as a Consequence of Uveitis?

Secondary glaucoma occurs in about 10 % of patients with uveitis and management is often challenging [28, 34]. Identifying the etiology of inflammation is an important step in managing a patient who presents with intraocular inflammation and increased intraocular pressure (IOP). A number of conditions that cause ocular inflammation may lead to blindness or even death if

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misdiagnosed; these include infectious endophthalmitis (endogenous or exogenous), intraocular foreign body, and tumors (lymphoma, melanoma).

Uveitis can be classified as acute or chronic (more than 3 months in duration). Anatomically, it can be divided into anterior (iridocyclitis), intermediate (e.g., pars planitis), posterior, and panuveitis categories. All patients presenting with uveitis need a detailed ocular and medical history with review of systems and a thorough eye examination, including dilated fundus examination. Patients presenting with a first episode of acute unilateral iridocyclitis or in the setting of a known systemic or ocular disease do not require laboratory investigations. However, if uveitis is bilateral, chronic, recurrent, granulomatous, or intermediate/posterior, a systemic work-up is indicated. This includes screening for ankylosing spondylitis (HLA-B27, sacroiliac joints X-ray), sarcoidosis (chest X-ray/CT, angiotensin converting enzyme level), syphilis (rapid plasma reactant or Venereal Disease Research Laboratory, and microhemagglutination-*Treponema pallidum* or fluorescent treponema antibody, absorbed), and tuberculosis (chest X-ray, PPD, and anergy panel). If a specific diagnosis is suspected based on history and examination, a more directed work-up should be performed.

Glaucoma occurs more commonly in *anterior* uveitis than in intermediate or posterior uveitis, and more commonly in *chronic* than in acute uveitis [28]. Some forms of chronic anterior uveitis have a particularly high rate of glaucoma, including Fuchs' heterochromic iridocyclitis (Fig. 48.1), Posner-Schlossman syndrome, herpetic keratouveitis, and juvenile rheumatoid arthritis associated uveitis.

Establishing a target IOP is an important step in the management of uveitic glaucoma. Often these patients do not have severe glaucomatous optic neuropathy and IOP elevations may be transient. In the setting of minimal or no optic nerve damage, a target IOP in the low 20s (mmHg) may be adequate (assuming average corneal thickness).

Summary for the Clinician

- Approximately 10 % of uveitis patients will develop secondary glaucoma.
- Glaucoma is more commonly seen in anterior uveitis and in chronic uveitis.
- Often uveitis patients have high IOP but healthy nerves. In these settings target IOPs in the low 20s may be adequate.

48.2 Is There a Way to Distinguish Between Elevated IOP Due to a Steroid Response vs. Uveitis?

Steroid-induced IOP elevation has been shown to occur with various routes of corticosteroid administration. However, most commonly it is caused by topical, periocular, intraocular, or systemic

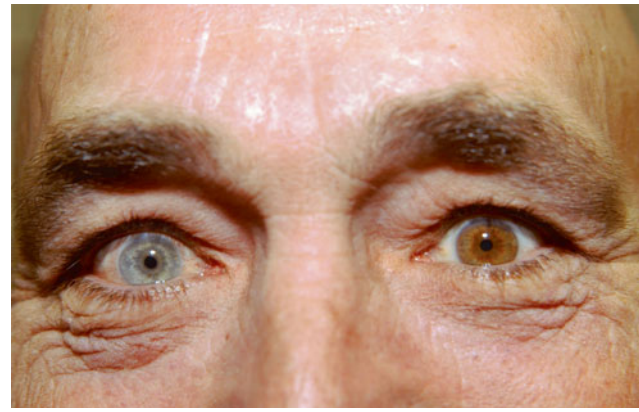

Fig. 48.1 Patient with Fuchs' heterochromic iridocyclitis in the right eye

Table 48.1 Comparison of IOP-elevating effect of various glucocorticoids and anti-inflammatory potency relative to hydrocortisone 0.5 %

Glucocorticoid	Relative potency	Rise in IOP (mmHg)
Dexamethasone 0.1 %	24	22
Fluorometholone 0.1 %	21	6
Prednisolone 1 %	2.3	10
Medrysone 1 %	1.7	1
Tetrahydrotriamcinolone 0.25 %	1.4	2
Hydrocortisone 0.5 %	1.0	3

steroid administration. Recently intravitreal and subtenon's injections of triamcinolone have become popular for the treatment of macular edema of different etiologies. These treatments can cause significant IOP elevations, at times requiring surgical intervention. A recent study found that the presence of uveitis was the strongest risk factor for IOP elevation after intravitreal injections of triamcinolone (odds ratio, 2.5; 95 % confidence interval 1.0–6.1) [18].

In general, the higher the anti-inflammatory potency of corticosteroid medications, the stronger the association with IOP elevation [7, 26]. Table 48.1 shows steroid potency relative to Hydrocortisone 0.5 % and the IOP-inducing effect of some commonly used ophthalmic steroid medications. Difluprednate ophthalmic solution 0.05 % (Durezol®; Alcon Laboratories, Fort Worth, TX) is a novel potent difluorinated prednisolone derivative [16]. In animal studies, difluprednate has a stronger glucocorticoid receptor-binding activity than prednisolone, betamethasone, or dexamethasone [49] and penetrates well into the anterior and posterior segment of the eye [49]. High potency and good penetration of difluprednate increase the risk of IOP elevation [16, 23]. Risk factors for steroid-induced IOP elevation are listed in Table 48.2 [24, 26]. In steroid-responsive patients, IOP elevation usually develops within the first few weeks of steroid administration [2, 3, 26]; however, IOP can elevate within hours of initial administration (this is rarely seen) [53] or many years after chronic steroid use [6]. After steroids are discontinued IOP usually normalizes within 1–4 weeks.

Table 48.2 Risk factors for steroid-induced IOP elevation

History of glaucoma, glaucoma suspect
First-degree relatives of glaucoma
Older age and children
High myopia
Type I diabetes
Connective tissue disease

Confusion can arise when an acute IOP elevation occurs after steroid treatment is initiated in the setting of uveitis. The IOP elevation may not be a true steroid-induced one, but rather secondary to decreased inflammation and improved ciliary body function, which in turn can lead to increased aqueous production overwhelming a dysfunctional trabecular meshwork (TM). It should be kept in mind that a true steroid-induced IOP elevation is rarely an acute elevation (i.e., IOP will not increase from 10 to 30 mmHg within a 24 h period but rather will occur more gradually). Steroid-induced glaucoma should also be on the differential diagnosis of normal tension glaucoma, as a resolved steroid-induced IOP elevation may have caused optic nerve damage that is apparent with currently low IOP measurements.

Some types of uveitis (e.g., herpetic keratouveitis, Posner-Schlossman) frequently cause IOP elevation. In these situations treatment with steroids will decrease inflammation and in turn the IOP.

Summary for the Clinician

- History of uveitis is a strong risk factor for IOP elevation after intravitreal injection of triamcinolone.
- In steroid-responsive patients, IOP elevation usually develops within the first few weeks following steroid administration; acute elevation of IOP secondary to steroids is very rare.
- After discontinuation of steroids, the IOP usually normalizes within 1–4 weeks.
- After initiation of steroids, inflammation may decrease and ciliary body

function may improve, which can cause a sudden increase in aqueous humor production and elevation of IOP (not a true steroid-response).
- History of steroid-induced glaucoma should be on the differential diagnosis of normal tension glaucoma.

48.3 How Do Inflammation and Steroids Cause an Increase in IOP?

The etiology of elevated IOP in uveitis is multifactorial. Intraocular inflammation affects IOP by altering aqueous production and/or outflow [34]. Low IOP can result from inflammation that usually causes the ciliary body to decrease aqueous production. However, in Posner-Schlossman syndrome, for example, it is believed that aqueous production is actually increased, possibly due to elevated levels of aqueous prostaglandins [36]. High IOP can result when inflammation leads to a decrease in aqueous outflow. This reduction can be either acute, which is often reversible, or chronic. In acute uveitis, TM outflow is decreased by either (1) inflammatory cells and/or fibrin, (2) swelling and dysfunction of the lamellar and endothelial cells (trabeculitis), or (3) uveal effusion or serous retinal detachment leading to angle-closure. In chronic uveitis, aqueous outflow is usually affected irreversibly by either (1) scarring or obliteration of the TM, (2) overgrowth of a fibro vascular membrane, or (3) synechial angle-closure. IOP can also be affected by central posterior synechiae leading to pupillary seclusion or inflammatory pupillary membranes that can lead to acute angle-closure.

It is generally believed that IOP elevation in steroid-induced glaucoma is secondary to a reduction in aqueous outflow facility [26, 54]. The precise mechanism by which this occurs is unknown, but several theories exist. Corticosteroids suppress phagocytosis of the trabecular endothelium that may lead to accumulation of aqueous debris in the meshwork and a decrease in the outflow facility. In perfusion-cultured human eyes, a dexamethasone-induced IOP increase was associated with thickening of trabecular beams and juxtacanalicular tissue, decrease in intertrabecular spaces, and an increase in the amorphous granular extracellular material [13, 28]. Several genes are upregulated in glucocorticoid-treated TM cells. The myocilin gene is the best studied and has been induced in human cultured TM cells exposed to dexamethasone [1, 33, 47]. It is also associated with the onset of juvenile and adult primary open angle glaucoma. However, in monkeys, there was no statistically significant link between myocilin mutations and steroid-induced ocular hypertension [15].

Summary for the Clinician

- Inflammatory glaucoma is usually secondary to a reduction in aqueous outflow that is either acute (blockage by cells, swelling, uveal effusion) or chronic (peripheral anterior synechiae, fibrovascular membrane).
- IOP elevation in steroid-induced glaucoma is secondary to the reduction of the aqueous outflow through incompletely understood mechanisms.

48.4 When Should I Operate on Uveitic Glaucoma?

Uveitic glaucoma is initially managed medically to decrease inflammation and IOP. A pearl of medical management is that the IOP reduction normally seen with glaucoma medications may be unpredictable in the inflamed eye. Beta blockers are effective in uveitis and usually are our first-line drug; however, IOP reduction may be less than the expected 30 % [28]. Topical and systemic carbonic anhydrase inhibitors (CAI) and selective α-adrenergic agonists can also be used. However, α-adrenergic agonists, similar to prostaglandin analogues (see the discussion below), may exacerbate ocular inflammation. Topical CAI may also inhibit corneal endothelial carbonic anhydrase and should be used with caution in patients with

corneal edema (see Chap. 47 for further explanation) [14, 29]. Miotic agents should be avoided in uveitis because of proinflammatory effects and the possibility of developing synechiae.

If acute angle-closure occurs due to a secluded pupil and pupillary block, laser peripheral iridotomy should be performed alongside dilation and anti-inflammatory medication. However, in a patient with active ongoing inflammation, an iridotomy may not remain patent [46]. In such cases, surgical iridectomy, possibly combined with synechiolysis of the secluded pupil, should be considered. Alternatively, more than one peripheral iridotomy can be performed to reduce the chance of recurrent pupillary block. In patients with less than 360° central posterior synechiae, it is reasonable to avoid iridotomy. Iridotomy will alter aqueous dynamics and may cause the remainder of the iris to scar down to the lens. In cases where there is significant inflammation, fibrin formation, and impending pupillary block from a secluded pupil, one can inject tissue plasminogen activator (TPA) (12.5 μm) in the anterior chamber [44, 47]. Such injection alone may be successful in breaking central posterior synechiae and avoiding surgical interventions [44].

In uveitic open angle or chronic angle-closure glaucoma, where there is chronically poorly controlled IOP on maximally tolerated medical treatment, surgery should be considered. There are two scenarios in which we recommend surgical intervention:

1. Significant optic nerve damage from chronic/intermittent IOP elevation requiring maximum medical management (e.g., Posner-Schlossman syndrome, herpetic keratouveitis, juvenile rheumatoid arthritis associated uveitis, steroid-response glaucoma).
2. Significant elevation of IOP despite maximum medical treatment, when there is a high risk of optic nerve damage, irrespective of the present degree of optic neuropathy.

Active intraocular inflammation will decrease the success rate of any surgical procedure. Therefore, if the IOP does not require immediate control, it is advisable to wait for approximately a 3-month inflammation-free period to pass before proceeding with surgery.

Summary for the Clinician

- Topical glaucoma medications should be used to control IOP when possible. However, glaucoma medications can have unpredictable effects on IOP in the setting of uveitis.
- It is important to recognize and treat pupillary block glaucoma in the setting of pupillary seclusion.
- Proceed to surgery with caution and a plan.

48.5 Is There a Preferred Surgery for Uveitic Glaucoma (Trabeculectomy vs. Tube vs. Laser)?

The currently accepted surgical options for treatment of glaucoma include trabeculectomy, tube shunt, or cyclophotocoagulation procedure. Laser trabeculoplasty is contraindicated in uveitic glaucoma, but may be tried in steroid-induced glaucoma [40]. Before proceeding with surgery, reversible causes, such as pupillary block, need to be ruled out.

In patients with uveitic glaucoma requiring surgery we often start with trabeculectomy with mitomycin C (MMC) or 5-fluorouracil (5-FU) (Fig. 48.2). There are situations, however, when the best surgical option is a tube shunt (see the discussion below), e.g., previous trabeculectomy or other conjunctival surgery, aphakia, scleromalacia, severe active inflammation.

Trabeculectomy with antiproliferative agents (either 5-FU or MMC) can be effective in the management of uveitic glaucoma. The long-term (7 months to 5 years) qualified success rate ranges from 50 to 85 % [8, 22, 38, 47, 50]. Most of these studies are retrospective reviews of patient records and often the investigators do

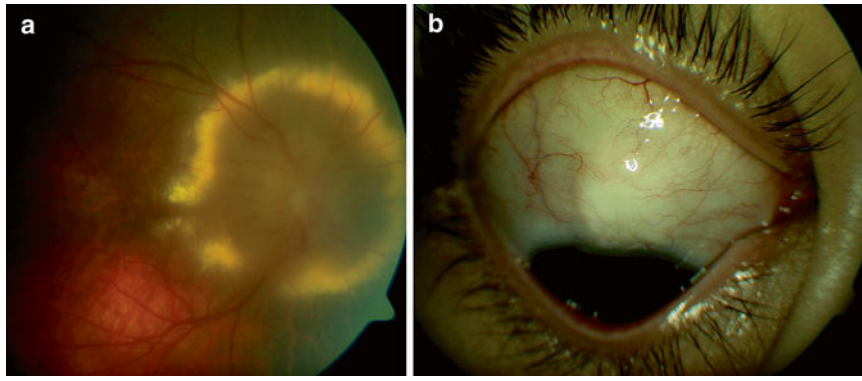

Fig. 48.2 23-year-old female with Vogt Koyanagi Harada syndrome with secondary glaucoma. (**a**) Fundus photograph of the right eye. (**b**) Superior conjunctival bleb 1 year after trabeculectomy with MMC (0.4 mg/mL applied for 2 min). IOP has remained 10–12 mmHg since the surgery on no glaucoma medication

not comment whether patients had active inflammation prior to surgery [8, 22]. However, Park and colleagues specifically state that in their study patients had to be in clinical remission for at least 3 months before they underwent phacotrabeculectomy with MMC [38]. The authors found that in their group the success rate was 84.8 % at 2 years. Towler et al. [50] observed that as in most trabeculectomy surgery, the success rate decreases with time. In their prospective study on the long-term outcome of trabeculectomy with 5-FU in uveitis-related glaucoma, the success rate decreased from 82 % at 1 and 2 years to 67 % at 5 years after the surgery.

Glaucoma secondary to childhood uveitis can be especially difficult to control. Recent studies found that in this group of patients (mostly with juvenile rheumatoid arthritis associated uveitis), goniotomy achieved successful IOP control in about 75 % of eyes of patients [17, 21]. There were few complications observed in the studies and some patients required postoperative glaucoma medications.

Cyclodestructive procedures should be used with caution in patients with uveitic glaucoma. They may exacerbate intraocular inflammation or cause an unexpected hypotony because of an already damaged ciliary body [35]. However, a cautious transscleral diode laser cyclophotocoagulation can be effective and safe in controlling refractory uveitic glaucoma [39, 42]. They are typically reserved for eyes with poor visual potential (≤20/200 vision). The role of endoscopic cyclophotocoagulation has not been specifically evaluated in patients with uveitic glaucoma. However, endoscopic cyclophotocoagulation, overall seems to be effective in controlling IOP in patients with refractory, including uveitic, glaucoma [10, 30, 31].

Summary for the Clinician

- Laser trabeculoplasty is contraindicated in uveitic glaucoma, but may be tried in steroid-induced glaucoma.
- It may be unnecessary to avoid trabeculectomy with antiproliferative agents.
- Cautious transscleral diode laser cyclophotocoagulation can be effective and safe in controlling refractory uveitic glaucoma.

48.6 Is One Tube Preferred over Another in Uveitic Glaucoma?

There are two main types of glaucoma shunts: valved and nonvalved. The most commonly used valved shunt is the Ahmed™ Glaucoma Valve

(New World Medical Inc., Cucamonga, CA). Currently, there are three models available: (1) Model S2—with a rigid polypropylene plate, (2) Model FP7—with a flexible silicone plate, and (3) Model M4. Each model also has bi-plate designs available. A commonly used nonvalved shunt is the Baerveldt glaucoma implant (Advanced Medical Optics, Inc., Santa Ana, CA). Currently, there are two models available: (1) Model BG 103-250 has a plate surface area of 250 mm^2 and (2) Model BG 101-350 has a plate surface area of 350 mm^2. Both Ahmed and Baerveldt shunts can be placed in either the anterior chamber or pars plana.

Overall, all shunts achieve safe and effective control of IOP in glaucoma [5, 11, 27]; however, the results are often not as good in uveitic glaucoma as in other types of glaucoma [32]. At present, there are no studies directly comparing the results of Ahmed and Baerveldt shunts in patients with uveitic glaucoma. In two retrospective studies of patients with refractory uveitic glaucoma, Ahmed shunts achieved satisfactory long-term IOP control (range 6–87 months) in 50–77 % of patients [19, 37]. The success rate decreased from 77 % at 1 year to 50 % at 4 years [37]. The number of patients not requiring glaucoma medication decreased from 50 % at 1 year to 26 % at 4 years [37]. The most common complications were corneal decompensation, encapsulated blebs, and transient hypotony. Similar results were reported in a smaller cohort of children ($n=6$, 7 eyes) with refractory uveitic glaucoma treated with Ahmed shunts: all seven (patients) eyes had IOP between 9 and 18 mmHg (average 12.1 mmHg) and the number of glaucoma medications decreased from an average of 3 to an average of 0.71 medications [25]. The only complication was hemorrhagic choroidal detachment in two (patients) eyes, which resolved in 1 month.

Baerveldt shunts overall have similar results to those of Ahmed shunts in uveitic glaucoma. On an average at 1–2 years, the success (with or without glaucoma medications) in controlling IOP ranges from 60 to 92 % [9, 32]. The most common complications are choroidal effusions (16.7 %), hypotony (12.5 %), and cystoid macular edema (12.5 %) [9].

Most studies comparing Baerveldt and Ahmed shunts in other types of refractory glaucoma found no significant difference in the effectiveness and complication rates [43, 48, 51]. However, a recent study comparing Baerveldt-250 with Ahmed S2 found that Ahmed S2 may be less effective at controlling long-term IOP and patients may require more glaucoma medications postoperatively [20].

Recently two multicenter randomized clinical trials, ABC and AVB studies, compared surgical outcomes of Baerveldt and Ahmed shunts in refractory glaucomas [4, 12]. Overall the 3-years follow-up results in these studies are similar [5, 11]. Both shunts produced a satisfactory decrease in IOP. However, the Baerveldt group had a higher success rate and required fewer glaucoma medications, but also experienced a higher rate of serious complications than the Ahmed group. While the results of the ABC and AVB studies are definitely helpful in general when deciding which shunt to use in a particular patient, only 7–10 % of patients enrolled in these studies had uveitic glaucoma. Therefore it is difficult to extrapolate these results when considering the surgical management of patients with uveitic glaucoma.

In the setting of refractory uveitic glaucoma, one can consider Baerveldt shunts (BG 101-350), unless the IOP is extremely high and requires immediate reduction. The theoretical advantages for the Baerveldt are (1) the bigger plate size associated with Baerveldt may lead to better long-term outcomes and (2) the possibility that the valve mechanism in any model of Ahmed shunt may become obstructed with inflammatory debris in patients with uveitic glaucoma. On the other hand, Baerveldt shunts may be associated with hypotony more frequently than Ahmed shunts, a complication which may be more common in patients with uveitic glaucoma.

Summary for the Clinician

- Overall, shunts achieve safe and effective control of IOP in uveitic glaucoma; however, the results are often not as good as in other types of glaucoma.
- There is no significant difference in the outcomes between Baerveldt and Ahmed shunts.

48.7 Do Prostaglandin Analogues Worsen Uveitic Inflammation?

Prostaglandin analogues are known to increase inflammation and sometimes may have a paradoxical effect on IOP [41]. Therefore, usually they are not our first-line treatment for uveitic glaucoma. However, recent studies have shown that prostaglandin analogues increase inflammation only in a small percentage of uveitis patients [45, 47, 52]. We usually start treatment with aqueous suppressants. However, if IOP remains elevated and the choice is between trying a prostaglandin analogue and proceeding with surgery, we do try a prostaglandin analogue, especially in acute cases when we expect IOP to stabilize over time. We try to avoid prostaglandin analogues in patients with history of or active cystoid macular edema, aphakia or herpetic eye disease.

Summary for the Clinician

- Prostaglandin analogues should not be the first-line agents in uveitic glaucoma.
- It is not necessary to avoid prostaglandin analogues unless patients have cystoid macular edema, aphakia, or herpetic eye disease.

48.8 Can One Expect a Greater Inflammatory Response in Uveitics After Glaucoma Surgery?

In general, the postoperative inflammatory response in uveitic eyes is greater. Significant inflammation following glaucoma surgery can lead to trabeculectomy scarring or tube obstruction and ultimate failure of the operation. In order to achieve good postoperative control of inflammation, it is important to control inflammation *preoperatively*. If necessary, we place patients on topical corticosteroids or even oral prednisone or immunomodulatory drugs preoperatively to control inflammation. Intraoperatively one may inject subtenon kenalog (40 mg) in addition to using topical postoperative steroids. It is helpful to consult with an internist or uveitis specialist for the perioperative control of inflammation in order to achieve optimal postoperative results.

Patients with uveitis are at risk of postoperative hypotony because of ciliary body shut-down. Hypotony by itself can increase postoperative inflammation and cause macular edema. Therefore, in these patients undergoing trabeculectomy we are careful to close the scleral flap more tightly than usual with judicious use of antifibrotic agent (5-FU or MMC) intraoperatively and laser suture-lysis postoperatively.

Summary for the Clinician

- The postoperative inflammatory response in uveitic eyes is greater.
- Control inflammation preoperatively.
- Consider consulting an internist or uveitis specialist for the perioperative control of inflammation to achieve optimal postoperative results.
- Uveitic eyes may have a damaged ciliary body with less-than-normal aqueous production. Avoid postoperative hypotony as much as possible by making adjustments to the surgical technique.

References

1. Alward WL. The genetics of open-angle glaucoma: the story of GLC1A and myocilin. Eye (Lond). 2000;14(Pt 3B):429–36.
2. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. Arch Ophthalmol. 1963;70:482–91.
3. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. II. The effect of dexamethasone in the glaucomatous eye. Arch Ophthalmol. 1963;70:492–9.
4. Barton K, Feuer WJ, Budenz DL, Schiffman J, Costa VP, Godfrey DG, Buys YM, Ahmed Baerveldt

Comparison Study Group. Three-year treatment outcomes in the Ahmed Baerveldt comparison study. Ophthalmology. 2014;121:1547–1557.e1541.
5. Barton K, Gedde SJ, Budenz DL, Feuer WJ, Schiffman J, Ahmed Baerveldt Comparison Study Group. The Ahmed Baerveldt Comparison Study methodology, baseline patient characteristics, and intraoperative complications. Ophthalmology. 2011;118:435–42.
6. Bernstein HN, Schwartz B. Effects of long-term systemic steroids on ocular pressure and tonographic values. Arch Ophthalmol. 1962;68:742–53.
7. Cantrill HL, Palmberg PF, Zink HA, Waltman SR, Podos SM, Becker B. Comparison of in vitro potency of corticosteroids with ability to raise intraocular pressure. Am J Ophthalmol. 1975;79:1012–7.
8. Ceballos EM, Beck AD, Lynn MJ. Trabeculectomy with antiproliferative agents in uveitic glaucoma. J Glaucoma. 2002;11:189–96.
9. Ceballos EM, Parrish II RK, Schiffman JC. Outcome of Baerveldt glaucoma drainage implants for the treatment of uveitic glaucoma. Ophthalmology. 2002;109:2256–60.
10. Chen J, Cohn RA, Lin SC, Cortes AE, Alvarado JA. Endoscopic photocoagulation of the ciliary body for treatment of refractory glaucomas. Am J Ophthalmol. 1997;124:787–96.
11. Christakis PG, Tsai JC, Kalenak JW, Zurakowski D, Cantor LB, Kammer JA, Ahmed II. The Ahmed versus Baerveldt study: three-year treatment outcomes. Ophthalmology. 2013;120:2232–40.
12. Christakis PG, Tsai JC, Zurakowski D, Kalenak JW, Cantor LB, Ahmed II. The Ahmed Versus Baerveldt study: design, baseline patient characteristics, and intraoperative complications. Ophthalmology. 2011;118:2172–9.
13. Clark AF, Wilson K, de Kater AW, Allingham RR, McCartney MD. Dexamethasone-induced ocular hypertension in perfusion-cultured human eyes. Invest Ophthalmol Vis Sci. 1995;36:478–89.
14. Epstein RJ, Brown SV, Konowal A. Endothelial changes associated with topical dorzolamide do appear to be significant. Arch Ophthalmol. 2004;122:1089, author reply 1090.
15. Fingert JH, Clark AF, Craig JE, Alward WL, Snibson GR, McLaughlin M, Tuttle L, Mackey DA, Sheffield VC, Stone EM. Evaluation of the myocilin (MYOC) glaucoma gene in monkey and human steroid-induced ocular hypertension. Invest Ophthalmol Vis Sci. 2001;42:145–52.
16. Foster CS, Davanzo R, Flynn TE, McLeod K, Vogel R, Crockett RS. Durezol (Difluprednate Ophthalmic Emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis. J Ocul Pharmacol Ther. 2010;26:475–83.
17. Freedman SF, Rodriguez-Rosa RE, Rojas MC, Enyedi LB. Goniotomy for glaucoma secondary to chronic childhood uveitis. Am J Ophthalmol. 2002;133:617–21.
18. Galor A, Margolis R, Brasil OM, Perez VL, Kaiser PK, Sears JE, Lowder CY, Smith SD. Adverse events after intravitreal triamcinolone in patients with and without uveitis. Ophthalmology. 2007;114:1912–8.
19. Gil-Carrasco F, Salinas-VanOrman E, Recillas-Gispert C, Paczka JA, Gilbert ME, Arellanes-Garcia L. Ahmed valve implant for uncontrolled uveitic glaucoma. Ocul Immunol Inflamm. 1998;6:27–37.
20. Goulet III RJ, Phan AD, Cantor LB, WuDunn D. Efficacy of the Ahmed S2 glaucoma valve compared with the Baerveldt 250-mm^2 glaucoma implant. Ophthalmology. 2008;115:1141–7.
21. Ho CL, Wong EY, Walton DS. Goniosurgery for glaucoma complicating chronic childhood uveitis. Arch Ophthalmol. 2004;122:838–44.
22. Jampel HD, Jabs DA, Quigley HA. Trabeculectomy with 5-fluorouracil for adult inflammatory glaucoma. Am J Ophthalmol. 1990;109:168–73.
23. Jeng KW, Fine HF, Wheatley HM, Roth D, Connors DB, Prenner JL. Incidence of steroid-induced ocular hypertension after vitreoretinal surgery with difluprednate versus prednisolone acetate. Retina. 2014;34:1990–6.
24. Jones III R, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. Curr Opin Ophthalmol. 2006;17:163–7.
25. Kafkala C, Hynes A, Choi J, Topalkara A, Foster CS. Ahmed valve implantation for uncontrolled pediatric uveitic glaucoma. J AAPOS. 2005;9:336–40.
26. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. Eye (Lond). 2006;20:407–16.
27. Kim J, Allingham RR, Hall J, Klitzman B, Stinnett S, Asrani S. Clinical experience with a novel glaucoma drainage implant. J Glaucoma. 2014;23:e91–7.
28. Kok H, Barton K. Uveitic glaucoma. Ophthalmol Clin North Am. 2002;15:375–87, viii.
29. Konowal A, Morrison JC, Brown SV, Cooke DL, Maguire LJ, Verdier DV, Fraunfelder FT, Dennis RF, Epstein RJ. Irreversible corneal decompensation in patients treated with topical dorzolamide. Am J Ophthalmol. 1999;127:403–6.
30. Lin S. Endoscopic cyclophotocoagulation. Br J Ophthalmol. 2002;86:1434–8.
31. Lin SC. Endoscopic and transscleral cyclophotocoagulation for the treatment of refractory glaucoma. J Glaucoma. 2008;17:238–47.
32. Lloyd MA, Baerveldt G, Fellenbaum PS, Sidoti PA, Minckler DS, Martone JF, LaBree L, Heuer DK. Intermediate-term results of a randomized clinical trial of the 350- versus the 500-mm^2 Baerveldt implant. Ophthalmology. 1994;101:1456–63, discussion 1463–4.
33. Lo WR, Rowlette LL, Caballero M, Yang P, Hernandez MR, Borras T. Tissue differential microarray analysis of dexamethasone induction reveals potential mechanisms of steroid glaucoma. Invest Ophthalmol Vis Sci. 2003;44:473–85.

34. Moorthy RS, Mermoud A, Baerveldt G, Minckler DS, Lee PP, Rao NA. Glaucoma associated with uveitis. Surv Ophthalmol. 1997;41:361–94.
35. Murphy CC, Burnett CA, Spry PG, Broadway DC, Diamond JP. A two centre study of the dose-response relation for transscleral diode laser cyclophotocoagulation in refractory glaucoma. Br J Ophthalmol. 2003;87:1252–7.
36. Nagataki S, Mishima S. Aqueous humor dynamics in glaucomato-cyclitic crisis. Invest Ophthalmol. 1976; 15:365–70.
37. Papadaki TG, Zacharopoulos IP, Pasquale LR, Christen WB, Netland PA, Foster CS. Long-term results of Ahmed glaucoma valve implantation for uveitic glaucoma. Am J Ophthalmol. 2007;144:62–9.
38. Park UC, Ahn JK, Park KH, Yu HG. Phacotrabeculectomy with mitomycin C in patients with uveitis. Am J Ophthalmol. 2006;142:1005–12.
39. Puska PM, Tarkkanen AH. Transscleral red laser cyclophotocoagulation for the treatment of therapy-resistant inflammatory glaucoma. Eur J Ophthalmol. 2007;17:550–6.
40. Ricci F, Missiroli F, Parravano M. Argon laser trabeculoplasty in triamcinolone acetonide induced ocular hypertension refractory to maximal medical treatment. Eur J Ophthalmol. 2006;16:756–7.
41. Saccà S, Pascotto A, Siniscalchi C, Rolando M. Ocular complications of latanoprost in uveitic glaucoma: three case reports. J Ocul Pharmacol Ther. 2001;17:107–13.
42. Schlote T, Derse M, Zierhut M. Transscleral diode laser cyclophotocoagulation for the treatment of refractory glaucoma secondary to inflammatory eye diseases. Br J Ophthalmol. 2000;84:999–1003.
43. Schwartz KS, Lee RK, Gedde SJ. Glaucoma drainage implants: a critical comparison of types. Curr Opin Ophthalmol. 2006;17:181–9.
44. Skolnick CA, Fiscella RG, Tessler HH, Goldstein DA. Tissue plasminogen activator to treat impending pupillary block glaucoma in patients with acute fibrinous HLA-B27 positive iridocyclitis. Am J Ophthalmol. 2000;129:363–6.
45. Smith SL, Pruitt CA, Sine CS, Hudgins AC, Stewart WC. Latanoprost 0.005% and anterior segment uveitis. Acta Ophthalmol Scand. 1999;77:668–72.
46. Spencer NA, Hall AJ, Stawell RJ. Nd:YAG laser iridotomy in uveitic glaucoma. Clin Experiment Ophthalmol. 2001;29:217–9.
47. Sung VC, Barton K. Management of inflammatory glaucomas. Curr Opin Ophthalmol. 2004;15:136–40.
48. Syed HM, Law SK, Nam SH, Li G, Caprioli J, Coleman A. Baerveldt-350 implant versus Ahmed valve for refractory glaucoma: a case-controlled comparison. J Glaucoma. 2004;13:38–45.
49. Tajika T, Waki M, Tsuzuki M, Kida T, Sakaki H. Pharmacokinetic features of difluprednate ophthalmic emulsion in rabbits as determined by glucocorticoid receptor-binding bioassay. J Ocul Pharmacol Ther. 2011;27:29–34.
50. Towler HM, McCluskey P, Shaer B, Lightman S. Long-term follow-up of trabeculectomy with intraoperative 5-fluorouracil for uveitis-related glaucoma. Ophthalmology. 2000;107:1822–8.
51. Tsai JC, Johnson CC, Kammer JA, Dietrich MS. The Ahmed shunt versus the Baerveldt shunt for refractory glaucoma II: longer-term outcomes from a single surgeon. Ophthalmology. 2006;113:913–7.
52. Warwar RE, Bullock JD, Ballal D. Cystoid macular edema and anterior uveitis associated with latanoprost use. Experience and incidence in a retrospective review of 94 patients. Ophthalmology. 1998;105: 263–8.
53. Weinreb RN, Polansky JR, Kramer SG, Baxter JD. Acute effects of dexamethasone on intraocular pressure in glaucoma. Invest Ophthalmol Vis Sci. 1985;26:170–5.
54. Wordinger RJ, Clark AF. Effects of glucocorticoids on the trabecular meshwork: towards a better understanding of glaucoma. Prog Retin Eye Res. 1999; 18:629–67.

Glaucomas: Neovascular Glaucoma

49

Adam S. Wenick and Alan L. Robin

Core Messages

- Anti-vascular endothelial growth factor (VEGF) therapy has become a standard part of treatment for NVG as a bridge to pan-retinal photocoagulation (PRP) and surgery.
- Prompt PRP or prompt anti-VEGF therapy with delayed PRP is vital to the preservation of vision in NVG.
- Glaucoma surgery should ideally be performed in an uninflamed eye with regressed neovascularization (NV), 2–3 weeks following PRP or sooner in eyes that have received anti-VEGF therapy. This may or may not be possible.
- Tube shunts are usually the preferred surgical technique in NVG, but trabeculectomy can be as effective in eyes with angle-closure and regressed NV. The supporting data for choice of surgical procedure is not strong.
- The most common cause of treatment failure in NVG is progression of underlying disease.
- A relatively small percentage of eyes undergoing long-term anti-VEGF therapy may show a significant increase in IOP requiring glaucoma therapy.

49.1 What Medications Can Be Used to Control Neovascular Glaucoma?

Topical and oral medical therapies are the initial treatment of choice to lower intraocular pressure (IOP) and limit vision loss and pain secondary to neovascular glaucoma (NVG).

49.1.1 IOP Lowering Agents

Therapies aimed at decreasing aqueous production (beta-blockers, topical and systemic carbonic anhydrase inhibitors, and alpha adrenergics) have the soundest rationale for use in NVG. No

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study is available in the literature comparing effectiveness of these various medications in NVG, and they are often required in combination. If the IOP were markedly elevated, it would not be inappropriate to commence therapy simultaneously with an alpha-agonist, topical nonselective beta-blocker, and topical carbonic anhydrase inhibitor.

The use of oral carbonic anhydrase inhibitors (acetazolamide) in place of or in combination with topical therapy (dorzolamide or brinzolamide) is often employed in the acute setting, and conflicting reports exist regarding their relative effectiveness. While Maus et al. [1] found oral acetazolamide to be more effective in reducing aqueous production and IOP than 2 % topical dorzolamide in normal subjects, Rosenberg et al. [2] found no difference in their effectiveness and no additive benefit of using both agents in combination in subjects with primary open angle glaucoma or ocular hypertension. Neither study found the combination of oral and topical carbonic anhydrase inhibitors to be more effective than oral therapy alone. It should be noted that both studies were performed in eyes with relatively normal anterior segments. The absorption and penetration of topical agents in eyes with an altered cornea, an altered anterior segment, and aqueous humor have not been well studied previously. It is unclear how these results extrapolate to NVG, where IOPs tend to be significantly higher than those in the studies cited above. Close monitoring of electrolytes should be employed with the long-term use of oral carbonic anhydrase inhibitors in this patient population that tends to have a high prevalence of concomitant renal disease, especially if patients are also taking thiazide or loop diuretics. It should be remembered that approximately two-thirds of subjects who use oral agents long term are unable to tolerate them due to systemic adverse events. Additionally there have been cases of Stevens-Johnson syndrome associated with the use of oral CAIs. Patients should be followed for this potential complication.

If the above therapies are ineffective, osmotic agents such as intravenous mannitol 1–2 g/kg can be used to further lower pressure in the acute setting for both the patient's comfort and to improve visualization of the angle. However, osmotics may have limited efficacy in NVG due to breakdown of the blood-vitreous barrier. Caution and close monitoring of serum electrolytes and renal function should be employed with these agents.

There is no data available regarding the use of prostaglandin analogues in NVG. Their effectiveness is uncertain as the uveal outflow path may be covered with neovascular membrane [3, 4]. Additionally, the use of prostaglandins could theoretically increase inflammation in NVG. However, if use of the other topical agents does not achieve sufficient pressure lowering effects, the use of prostaglandin analogues should be considered, as they may be effective and spare the patient possible systemic side effects that can occur with osmotic agents or oral acetazolamide.

There is no role for the use of topically administered muscarinic agents, as closed angles or membranes covering the trabecular meshwork render them ineffective [3]. Not only is IOP not typically lowered by these agents, but they may cause increased inflammation and discomfort [4, 5] and worsen synechial angle-closure [4].

49.1.2 Anti-inflammatory and Anti-angiogenic Medications

Frequent administration of topical corticosteroid medications are recommended to reduce inflammation that is inevitably present [3]. There is minimal data on the role of oral steroids for this purpose, and it must be remembered that oral steroids could have significant adverse effects in diabetic patients.

Intravitreal corticosteroid injections have also been proposed as a useful adjunct to therapy or as primary therapy in the treatment of NVG [6]. Jonas et al. treated four eyes with NVG caused by central retinal vein occlusion (CRVO) or proliferative diabetic retinopathy (PDR) with injection of 20 mg of crystalline triamcinolone acetonide alone and found that all four eyes had a marked decrease in rubeosis iridis with lowering of mean IOP from 26.5 ± 12.1 to 21.75 ± 11.3 mmHg.

However, one of these eyes with initial IOP of 40 mmHg demonstrated no decrease in IOP after injection [6]. The use of intravitreal steroids remains unproven and no large-scale trials have yet confirmed these initial results.

The use of oral, topical, periocular, or intraocular steroids is certainly indicated for the treatment of the underlying disease in NVG caused by inflammation. Antivascular endothelial growth factor (VEGF) therapy has become an important adjunct in the treatment of NVG and is discussed further below.

49.1.3 Cycloplegics/Mydriatics

Topical atropine sulfate 1 % may be used for symptomatic relief of pain in NVG. It may also have some effect in lessening inflammation [7] and possibly in increasing aqueous outflow through the uveoscleral route, if this pathway is not blocked by fibrovascular membranes [4]. It may also help maximize the view of the fundus if there is no hyphema or vitreous hemorrhage present. If posterior synechiae do occur, the use of these agents will allow for a larger pupil.

IOP lowering alone may decrease ischemia and therefore decrease the stimulus for neovascularization (NV) [8]; but prompt medical or laser treatment of the underlying disorder is critical to prevent formation of peripheral anterior synechiae (PAS) and angle-closure. Once extensive PAS have formed, surgical treatment is usually required to control IOP, despite regression of NV, as topical agents are rarely sufficiently effective once PAS have formed.

Summary for the Clinician

- Aqueous suppressants, beta-blockers, carbonic anhydrase inhibitors (topical and oral), and alpha adrenergics are the mainstay of treatment for the lowering of IOP in NVG.
- Oral and intravenous acetazolamide and intravenous mannitol may be used with caution in the patient population due to a high prevalence of concomitant renal disease.
- Intense topical corticosteroids are recommended to quell the prominent inflammatory response in NVG.
- Topical atropine is also recommended for symptomatic relief and may decrease IOP and inflammation in NVG.
- Failure of medical therapy alone is the rule in advanced NVG.

49.2 What Is the Surgical Treatment of Choice for Neovascular Glaucoma?

The three modalities most often employed when medical treatment fails to control IOP in NVG are tube shunts, trabeculectomy, and cycloablation. There is no role for laser trabeculoplasty, iStents, Trabectomes, or other minimally invasive glaucoma surgeries in these highly abnormal angles. Almost 30 years ago, Simmons et al. attempted to actually coagulate the angle's vessels, but produced vascular spasm and minimal long-term coagulation [9, 10].

Understanding the pathogenesis and disease course of NVG is vital to understanding the surgical choices and reasons for surgical failures. In the initial stages of NVG, fibrovascular tissue grows over the trabecular meshwork leading to decreased aqueous outflow and increased IOP. Next, myofibroblasts present in the neovascular tissue proliferate and contract, leading to progressive permanent angle-closure and progressive increase in IOP. Corneal endothelial proliferation can also extend over the angle [11]. When deciding upon the best surgical option for a patient who has failed medical therapy and when analyzing the surgical literature, it is important to keep the above in mind and note that NVG is not a homogenous disease.

Surgical failure in NVG is usually defined as an inability to control IOP, as well as the development

of phthisis and/or loss of light perception, regardless of the specific etiology of the latter. While phthisis and loss of light perception can occur from glaucomatous damage due to high IOP or as a complication of glaucoma surgery, progression of underlying ischemic disease, rather than failure to control IOP, is the most common cause of failure of surgeries for NVG [12]. It is therefore important to interpret study results in the context of the natural history of the underlying disease. Anti-VEGF therapy has been shown to decrease and even lead to reversal of retinal nonperfusion in the setting of diabetic retinopathy as well as retinal vein occlusion [13–15]. Therefore, the introduction of the widespread use of anti-VEGF therapy for treatment of macular edema in ischemic retinal disease may lead to better outcomes for cases of NVG than those reported prior to the availability of anti-VEGF therapy. This possibility warrants further exploration with more current prospective or retrospective studies.

The ideal surgical treatment is influenced by the underlying disorder as well as the clinical characteristics of each patient, i.e., IOP, presence of active vs. regressed NV, prior laser or VEGF therapy, prior intraocular surgical therapies, degree of inflammation, degree of angle-closure, presence of hazy ocular media, and visual potential. Outcomes tend to be better in PDR compared to CRVOs [16], and ocular ischemic syndrome has the worst prognosis [3].

A majority of the literature concerning the surgical treatment of NVG consists of retrospective noncomparative case series [4]. Few comparative series and no prospective comparative studies or randomized trials exist in the literature (Tables 49.1 and 49.2). Comparing techniques in these different series is impossible due to different measures of successful outcome, differing and insufficient follow-up times, and different baseline patient characteristics, including differences in etiology of NVG, baseline visual function, degree of NVA and PAS, and percentage of patients who have undergone pan-retinal photocoagulation (PRP). In many of these reports, all of these details are not even available.

Early studies with cyclocryoablation reported a large percentage of patients with vision loss and phthisis [17], relegating the use of cyclocryoablation and cyclophotocoagulation only to eyes with limited visual potential [4]. These early studies did not employ graduated cycloablation, which results in better outcomes [18, 19], and which some advocate as primary therapy for some cases with good visual potential [3]. The bias towards using cycloablation only in eyes with poor visual potential, combined with the retrospective nature of studies in the literature has led to a reinforcement of the belief that cycloablation should only be used when visual prognosis is poor. Eid et al. found better outcomes with tube shunts compared to cyclophotocoagulation in a retrospective study in which patients were matched in terms of underlying disease. However, in the cyclophotocoagulation group only 4.2 % of patients had a visual acuity better than count fingers, while in the tube shunt group 41.7 % of patients had vision better than count fingers. Additionally, a larger proportion of patients in the cyclophotocoagulation group had 360° of angle-closure [20], bringing the conclusions of this report into question. Further concern over the use of cyclophotocoagulation for treatment of NVG comes from a recent study showing an increased risk of hypotony when transscleral diode laser cyclophotocoagulation is used for the treatment of NVG compared to the treatment of other types of glaucoma [21]. The level of concern that should be inferred from this study is uncertain due to the study's retrospective nature as well as the fact that outcomes with other surgical techniques are also inferior in the setting of NVG compared to other types of refractory glaucoma [22]. Currently, most glaucoma specialists recommend cyclophotocoagulation only in eyes with poor visual prognosis or when other methods have failed to control IOP. However, further studies are needed to evaluate the role of graduated cyclophotocoagulation in NVG, as some promising results have been published [19].

A study by Tsai et al. reporting poor long-term results of trabeculectomy with 5-FU in NVG—5 year survival rate of filtering surgery with 5-FU was only 28 %—is often cited as a rational for using tube shunts rather than trabeculectomy for NVG [11]. However these results are similar to long-term results with tube shunts (Tables 49.1 and 49.2) [16, 23]. The use of

Table 49.1 Studies of NVG and tube shunt surgery

Study	Mermoud et al. [16]	Yalvac et al. [23][a]	Yalvac et al. [23][a]	Susanna et al. [62]	Krupin et al. [5]	Krupin et al. [63]	Sidoti et al. [8]	Eid et al. [20][a]	Minkler et al. [64]	Lloyd et al. [65]	Downes et al. [66]	Freedman et al. [67]	Anker et al. [68]	Faghihi et al. [69]	Chalam et al. [70][a]
Technique	Molteno	Ahmed	Molteno	Ahmed + MMC	Krupin	Krupin	Baerveldt	Tube shunt[b]	Molteno	Molteno	Molteno	Molteno	Molteno	PPV + Ahmed	PPV + Baerveldt
Number of patients (eyes)	54(60)	38(38)	27(27)	92(92)	40(40)	79(79)	36(36)	24(24)	15(15)	18(18)	50(50)	18(18)	36(36)	17(18)	18(18)
Mean age	61.8	57.7	58.3	60.6	49	55.9	62	68.4	59.5	58.8	54.3	NR	55.4	49	70
Mean follow-up (months)	24.7	37	41.9	12	13.8	23.7	15.7	15.2	20.2	33.8	29.5	35	15.5	14.2	6
Criteria for success	IOP < 22[c]	IOP 6–21[c]	IOP 6–21[c]	IOP 5–21[d]	IOP < 25[c]	IOP < 25[c]	IOP 6–21[c]	IOP 6–25[c]	<22[c]	IOP 6–21[c]	IOP < 26[c]	IOP < 22[c]	<20[e]	IOP 5–21[c]	IOP 6–21
PRP/cryo (%)	65	94.7	92.6	NR	NR	NR	NR	70.8	73.3	77.8	24	NR	NR	100	0
DR	53	50	55.6	NR	55	75	53	41.7	60	67	64	NR	31	67	66.7
RVO	40	44.7	37	NR	30	15	28	41.7	27	22	36	NR	50	28	22.2
Other	7	5.2	7.4	NR	15	10	19	16.7	13	11	0	NR	19	5	11.1
Percentage of success[f]	62.1, 52.9, 43.1, 30.8, 10.3[g]	63.2, 56.2, 43.2, 37.8, 25.2[g]	37.0, 29.6, 29.6, 29.6, 29.6[g]	74.2	68	67	79, 56[h]	66.7	47	22	60	66.7	66.7	72.2	94.4

NR data not reported
[a]Comparative study
[b]Molteno, Ahmed, Baerveldt, or Schocket
[c]±IOP lowering drops, no phthisis, no further surgery
[d]With at least 30 % reduction in IOP, ±IOP lowering drops, no phthisis
[e]Without medications
[f]Differences in format of reported outcomes related to format of data presentation in original publications
[g]Kaplan-Meier life-table success at 1, 2, 3, 4, 5 years
[h]Kaplan-Meier life-table success at 12 and 18 months

Table 49.2 Studies of NVG and filtering surgery

Study	Allen et al. [7]	Euswas et al. [30]	Mandal et al. [29]	Kiuchi et al. [27]	Herschler et al. [71]	Elgin et al. [12]	Tsai et al. [11]	Flanagan et al. [25]	Clearkin et al. [26]	Lee et al. [72]	Fernandez-Vigo et al. [73]	Kiuchi et al. [74] PG	Kiuchi et al. [74]PC	Kono et al. [75]
Technique	Trab/PLS	TMMC	TMMC	TMMC	Trab	TMMC + iris cauterization	Trab/PLS + 5-FU	Trab	Trab	Modified Trab	Trab	PPV+		PPV + filtering
Number of patients (eyes)	22(24)	21(23)	14(15)	35(35)	13(13)	72(72)	34(34)	6(6)	6(6)	5(5)	23(26)	9(9)	16(16)	18(21)
Mean age	51.4	59.7	59.9	59.1	53.8	53.8	51.5	37.3	64	55.6	53	54.7	57.9	66.1
Mean follow-up (months)	22.8	29	28.6	25.6	18	6	12.5	6	12	13.4	NR	26.9	31	36.5
Criteria for success	IOP < 25[a]	IOP < 22[a]	IOP < 22[b]	IOP < 22[a]	IOP 6–26[c]	IOP < 23[a]	IOP < 22[a]	useful vision	IOP < 22[a]	IOP 4–20[a]	IOP < 23[c]	IOP < 22[a]	IOP < 22[a]	IOP 5–21[a]
PRP/cryo (%)	71	100[d]	87	48.5	NR	100	85	100	100	NR	100	100	100	100
DR	71	43.5	53	100	61.5	59.7	71	33.3	0	60	100	100	100	62
RVO	21	43.5	40	0	23.1	37.5	21	66.7	100	40	0	0	0	38
Other	8	13	7	0	15.4	2.8	9	0	0	0	0	0	0	0
Percentage of success[e]	67	91.3	67	67, 61.8, 61.8[f]	77	66	71, 67, 61, 41, 28[g]	100	100	100	77, 27[h]	55.6, 18.5, NR	81.3, 81.3, 81.3[f]	90.5

PLS posterior lip sclerotomy, *TMMC* trabeculectomy with mitomycin C, *NR* data not reported, *PG* proliferative group-vitreous hemorrhage, fibrovascular membrane, and/or retinal detachment, *PC* NVG but no vitreous hemorrhage, fibrovascular membrane, or retinal detachment

[a]±IOP lowering drops, no phthisis, no further surgery

[b]Without medications

[c]±IOP lowering drops, allowed additional surgery

[d]After filtering surgery

[e]Differences in format of reported outcomes related to format of data presentation in original publications

[f]Kaplan-Meier life-table success at 12, 24, and 36 months

[g]Kaplan-Meier life-table success at 1, 2, 3, 4, 5 years

[h]Percentage success at 12 and 24 months

mitomycin C (MMC) may give superior results to 5-FU, though one small study found no difference between the two antimetabolites in NVG [24]. As mentioned above, failure of glaucoma surgery in NVG is most commonly caused by progression of underlying disease, and poor outcomes at 5 years may represent progressive ischemia rather than problems intrinsic to any one technique. In uninflamed NVG eyes treated with previous PRP and/or anti-VEGF therapy, NVG becomes similar to uncomplicated angle-closure and better results can be expected with trabeculectomy [25, 26]. That being said, younger eyes [11] and eyes with prior vitrectomy [27] tend to fare worse with trabeculectomy. The ability of anti-VEGF agents to induce rapid regression of NV of the angle and iris (discussed below) warrants further exploration for an expanded role for trabeculectomy in NVG. Newer well-designed prospective studies are needed to better understand surgical outcomes in eyes receiving anti-VEGF therapy, which may greatly increase the surgical success rate.

As noted above, for many glaucoma specialists, tube shunts have become the treatment of choice for NVG. While trabeculectomy is a viable option in quiet eyes with regressed NV, tubes shunts seem to be a better choice in inflamed eyes where failure rates of trabeculectomy are highest. While many advocate the use of one type of tube over others, the results with different devices are roughly equivalent [28] (see Table 49.1). As with trabeculectomy, tube shunt results are worse when used for NVG than for other types of glaucoma [22]. It is recommended that tube shunts be placed as far posterior as possible, i.e., at the pars plana in eyes that have undergone vitrectomy and in the sulcus in pseudophakic eyes. This will help to avoid corneal decompensation and blockage of tubes from neovascular membranes.

Summary for the Clinician

- Comparison of surgical techniques to treat NVG is severely limited due to a dearth of comparative and prospective studies using different outcome measures.
- Though tube shunts are considered by many to be the surgical treatment of choice in NVG, trabeculectomy and tube shunts are likely equivalent in quieter eyes with regressed NV.
- Tubes shunts or cycloablation are more likely than trabeculectomy to be effective in inflamed eyes with active NV.
- Cycloablation is most often employed only in eyes with poor visual potential, but graduated cyclophotocoagulation may have a primary role in treatment of eyes with good visual potential, and its use may be further investigated.
- Over the long term, all surgical techniques share poor outcomes in NVG in large part due to progression of underlying disease. This trend may be improved with anti-VEGF therapy.

49.3 How Should PRP and Glaucoma Surgery Be Timed?

Determining the timing of PRP with relation to surgery must take into account the characteristics of the individual patient's disease. Factors such as media opacities and significantly elevated IOP, despite maximal medical therapy, may lead to glaucoma surgery sooner than would otherwise be desired.

Ideally if given the luxury, filtering or tube implant surgery should be done in eyes following regression of iris and angle NV and following a decrease in ocular inflammation, which will reduce the rates of intraoperative complications (hyphema) and early complications due to a prominent inflammatory response (such as bleb failure) [7, 12, 25, 29]. This favorable response is usually seen within 2–3 weeks following PRP and, as discussed below, can be seen even sooner following anti-VEGF therapy.

Eyes with previously healthy optic nerves likely can tolerate IOP in the mid 30s during this relatively short period following PRP. Already

severely damaged optic nerves, from asymptomatic IOP elevation or from POAG for instance, may not be able to tolerate these same IOPs for 2–3 weeks without further significant optic neuropathy [7]. Inability to control IOP to at least these levels (the mid 30s) is an indication for relatively prompt glaucoma surgery. The clinician must also keep in mind that PRP can rarely lead to a further increase in IOP [3], necessitating close follow-up in the interim period.

Even in the absence of anti-VEGF therapy or the ability to perform PRP due to hazy ocular media, promising results have been reported with delay of PRP until at least 1 week after trabeculectomy with mitomycin-C [30]. In this consecutive series of 21 patients and 23 eyes, a qualified success rate of 91.3 % was seen with follow-up of 12–47 months (mean 29 ± 11.3) [30].

The availability of anti-VEGF therapy has also allowed for a different approach for the timing of PRP and glaucoma surgery. PRP in the setting of elevated IOP and inflammation related to NVG can be quite painful and may necessitate a retrobulbar block in the acute setting. In cases were the patient is unable to tolerate PRP in the clinic, the ability of anti-VEGF therapy to induce rapid regression of NVI and NVA (discussed below) also allows for deferral of PRP in the short term until the time of glaucoma surgery. At this time, indirect laser PRP can then be performed with the patient under anesthesia immediately prior to the glaucoma procedure.

Summary for the Clinician

- In the absence of anti-VEGF therapy, PRP should precede glaucoma surgery by 2–3 weeks, whenever possible, to allow for regression of NV prior to surgical intervention.
- Prompt anti-VEGF therapy followed by delayed concurrent indirect laser PRP and glaucoma surgery is another option for therapy.

49.4 What Kind of Results and Time-Course Can I Expect from the Use of Anti-VEGF Drugs? Should It Be Injected into the Anterior Chamber or Vitreal Cavity?

Anti-VEGF therapy has become a mainstay in the treatment of NVG. Multiple case series have been published showing rapid regression of NVI and NVA following treatment with intravitreal and intracameral bevacizumab (Figs. 49.1 and 49.2) in cases of NVG secondary to PDR, CRVO, ocular ischemic syndrome, and radiation retinopathy [31–42] (Table 49.3). Similar results have been reported with intracameral and intravitreal ranibizumab [43, 44] and would be expected as well with aflibercept. A number of case series [45, 46], retrospective comparative case series [47, 48], and two small prospective randomized trials [49, 50] have also been reported detailing the use of anti-VEGF therapy as an adjunct at the time of glaucoma surgery. While a number of these studies showed decreased rates of hyphema and persistent neovascularization with the addition of anti-VEGF therapy, only a single study has reported improved outcomes with anti-VEGF therapy [50].

Following anti-VEGF therapy, rapid and usually complete regression of NVI and NVA occurs, often within 24–48 h [31, 32, 34, 36]. This regression is associated with reduction in pain and, if synechial angle closure is not present, with decreased IOP or in some cases normalization of IOP [34, 36]. Without the addition of PRP, given the duration of action of anti-VEGF therapy, neovascularization could recur as soon as several weeks to a month following treatment. However, the rates and time course for the recurrence of NVI and NVA following anti-VEGF therapy in the absence of PRP have not been well described. Anti-VEGF therapy in the setting of NVG appears to be safe, though the rare complication of central retinal artery occlusion has been reported following injection in the setting of NVG. Both reported cases were in cases of ocular ischemic syndrome [51].

Fig. 49.1 Bevacizumab prepared for intravitreal injection by the chemotherapy pharmacist

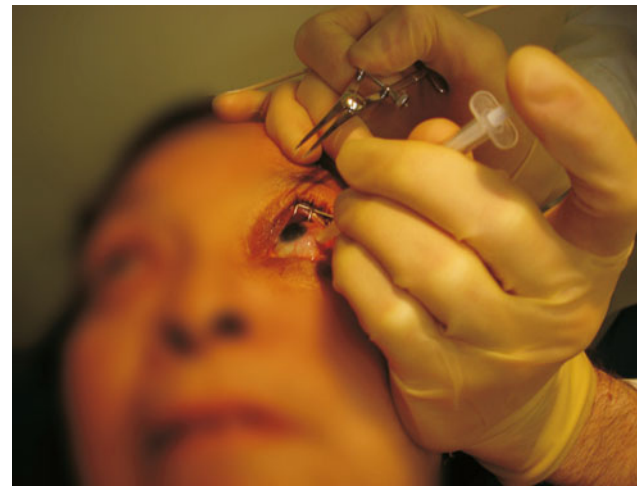

Fig. 49.2 A patient receiving intravitreal bevacizumab for neovascularization of the angle and iris due to proliferative diabetic retinopathy

As noted above, regression of anterior segment neovascularization has been reported following intravitreal, anterior chamber, and posterior chamber injection of an anti-VEGF agent. It has also been described following subconjunctival [52] and topical administration [53]. When determining which route of administration should be employed, consideration of the underlying causative disease as well as the experience of the physician performing the

Table 49.3 Doses used for anti-VEGF therapy in neovascular glaucoma

Anterior segment dose
Bevacizumab 1.25 mg/0.05 mL or 1.00 mg/0.04 mL
Ranibizumab 0.5 mg/0.05 mL or 0.4 mg/0.04 mL
Ranibizumab 0.3 mg/0.05 mL or 0.24 mg/0.04 mL
Aflibercept 2 mg/0.05 mL or 1.6 mg/0.04 mL
Intravitreal dose
Bevacizumab 1.25 mg/0.05 mL
Ranibizumab 0.5 mg/0.05 mL
Ranibizumab 0.3 mg/0.05 mL
Aflibercept 2 mg/0.05 mL

procedure must be considered. While intravitreal injections have become the most commonly performed procedure by retina specialists, other ophthalmologists may have limited experience with this procedure. That being said, the intravitreal route is often the preferred route for several reasons. First, the patient may have an underlying retinal condition such as macular edema from DR or RVO or retinal neovascularization that would also benefit from intravitreal administration of the anti-VEGF agent. For this reason, prior to administration of anti-VEGF therapy for NVG, a thorough examination of the posterior segment, including B-scan ultrasound in cases with opaque ocular media, is recommended in cases of NVG both to determine the etiology of NVG as well as to assess for additional complications that should be treated. When using intravitreal or intracameral anti-VEGF therapy, it is important to keep in mind the short-term elevation in IOP that may occur after injection [54]. The need for anterior chamber paracentesis following intravitreal or anterior segment administration is the norm in eyes that already have markedly elevated IOP. Injection into the separate compartment and larger space of the vitreal cavity offers the advantage of having a higher dose of the medication present in the eye, especially after paracentesis, possibly leading to a longer duration of action. One should keep in mind that hemorrhagic complications (including commonly hyphema and rarely suprachoroidal hemorrhage) may occur with acute reduction of IOP by paracentesis. Because of the common occurrence of hyphema with paracentesis in the setting of NVG, PRP should be performed prior to administration of the anti-VEGF agent while the media is clear.

Summary for the Clinician

- Despite limited data showing superior outcomes in NVG with the use of anti-VEGF agents, due to its ability to cause rapid regression of NVI and NVA, anti-VEGF therapy is now an important adjunct for the treatment of NVG.
- Results can be expected in as little as 24–48 h after injection of an anti-VEGF agent.
- Despite the dramatic effects that anti-VEGF therapy has on the regression of NVI and NVA, surgery usually is required if significant permanent angle-closure has developed.
- Intraocular anti-VEGF therapy is most useful as a bridge to or adjunct to PRP and glaucoma surgery rather than a definitive treatment for NVG.

49.5 What Effects Do Chronically Injected Anti-VEGF Drugs Have on IOP?

Original reports from the MARINA [55] and ANCHOR [56] studies in which eyes with new onset neovascular age-related macular degeneration were treated with ranibizumab every 4 weeks for 2 years compared to sham injection or photodynamic therapy, respectively, did not indicate a significant incidence in ocular hypertension in the eyes treated with ranibizumab. With more widespread use of anti-VEGF agents, cases of significant elevation of IOP have been reported with both ranibizumab and bevacizumab [54, 57–59]. Subsequent analysis of the IOP data from MARINA and ANCHOR with a less stringent definition of ocular hypertension did reveal slightly higher rates of elevated IOP in the ranibizumab treated groups, but these effects appeared

to be small [60]. In the two ranibizumab treatment groups, 37.0 and 39.9 % of patients had a single post-injection IOP measurement greater than or equal to 21 mmHg compared to 29.1 % in the sham/PDT arm; 11.5 and 10.9 % had a single measurement of IOP of greater or equal to 25 mmHg compared to 5.1 % in the control arms, but no significant difference was noted when considering IOP of 30 mmHg or greater. Only 0.8–2.1 % had an IOP greater than or equal to 30 mmHg on a single visit and no patients had an IOP greater than or equal to 30 mmHg on more than two visits. Other reports have indicated that patients with a history of glaucoma are more likely to have an elevation of IOP with anti-VEGF therapy [57, 61].

While several theories have been put forth, the mechanisms responsible for this elevation of IOP are unknown. The percentage of patients affected and the level of IOP elevation are significantly less than that seen with intravitreal steroid therapy. Overall, chronic anti-VEGF therapy has been shown to cause a mild increase in IOP in a relatively small number of patients. Significant elevation of IOP in the setting of anti-VEGF therapy has been reported but is rare. The potential for elevation of IOP is rarely a reason to withhold anti-VEGF therapy given the high risk of vision loss from retinal disease. These findings do, however, warrant close monitoring of IOP in patients undergoing anti-VEGF therapy.

Summary for the Clinician

- A relatively small percentage of eyes undergoing long-term anti-VEGF therapy show a significant increase in IOP requiring glaucoma therapy with a higher but still small percentage of eyes showing mild elevation of IOP.
- The incidence of elevated IOP in the setting of chronic anti-VEGF therapy may be higher in eyes with preexisting glaucoma.
- Given the significant visual benefits of anti-VEGF therapy when used appropriately, elevation of IOP would rarely be an indication to withhold therapy, but close monitoring of IOP is necessary for patients undergoing anti-VEGF therapy.

References

1. Maus TL, et al. Comparison of dorzolamide and acetazolamide as suppressors of aqueous humor flow in humans. Arch Ophthalmol. 1997;115(1):45–9.
2. Rosenberg LF, et al. Combination of systemic acetazolamide and topical dorzolamide in reducing intraocular pressure and aqueous humor formation. Ophthalmology. 1998;105(1):88–92, discussion 92–3.
3. Hayreh SS. Neovascular glaucoma. Prog Retin Eye Res. 2007;26(5):470–85.
4. Sivak-Callcott JA, et al. Evidence-based recommendations for the diagnosis and treatment of neovascular glaucoma. Ophthalmology. 2001;108(10):1767–76, quiz 1777, 1800.
5. Krupin T, et al. Filtering valve implant surgery for eyes with neovascular glaucoma. Am J Ophthalmol. 1980;89(3):338–43.
6. Jonas JB, et al. Regression of neovascular iris vessels by intravitreal injection of crystalline cortisone. J Glaucoma. 2001;10(4):284–7.
7. Allen RC, et al. Filtration surgery in the treatment of neovascular glaucoma. Ophthalmology. 1982;89(10):1181–7.
8. Sidoti PA, et al. Experience with the Baerveldt glaucoma implant in treating neovascular glaucoma. Ophthalmology. 1995;102(7):1107–18.
9. Simmons RJ, Deppermann SR, Dueker DK. The role of gonio-photocoagulation in neovascularization of the anterior chamber angle. Ophthalmology. 1980;87(1):79–82.
10. Simmons RJ, et al. Goniophotocoagulation for neovascular glaucoma. Trans Sect Ophthalmol Am Acad Ophthalmol Otolaryngol. 1977;83(1):80–9.
11. Tsai JC, et al. 5-Fluorouracil filtering surgery and neovascular glaucoma. Long-term follow-up of the original pilot study. Ophthalmology. 1995;102(6):887–92, discussion 892–3.
12. Elgin U, et al. Trabeculectomy with mitomycin C combined with direct cauterization of peripheral iris in the management of neovascular glaucoma. J Glaucoma. 2006;15(5):466–70.
13. Campochiaro PA, et al. Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion. Ophthalmology. 2013;120(4):795–802.

14. Campochiaro PA, et al. Neutralization of vascular endothelial growth factor slows progression of retinal nonperfusion in patients with diabetic macular edema. Ophthalmology. 2014;121(9):1783–9.
15. Sophie R, et al. Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion. Am J Ophthalmol. 2013;156(4):693–705.
16. Mermoud A, et al. Molteno tube implantation for neovascular glaucoma. Long-term results and factors influencing the outcome. Ophthalmology. 1993;100(6):897–902.
17. Krupin T, Mitchell KB, Becker B. Cyclocryotherapy in neovascular glaucoma. Am J Ophthalmol. 1978; 86(1):24–6.
18. Chang SH, et al. Contact diode laser transscleral cyclophotocoagulation for refractory glaucoma: comparison of two treatment protocols. Can J Ophthalmol. 2004;39(5):511–6.
19. Delgado MF, et al. Long-term results of noncontact neodymium:yttrium-aluminum-garnet cyclophotocoagulation in neovascular glaucoma. Ophthalmology. 2003;110(5):895–9.
20. Eid TE, et al. Tube-shunt surgery versus neodymium:YAG cyclophotocoagulation in the management of neovascular glaucoma. Ophthalmology. 1997;104(10):1692–700.
21. Ramli N, et al. Risk factors for hypotony after transscleral diode cyclophotocoagulation. J Glaucoma. 2012;21(3):169–73.
22. Das JC, et al. The Ahmed Glaucoma Valve in refractory glaucoma: experiences in Indian eyes. Eye. 2005;19(2):183–90.
23. Yalvac IS, et al. Long-term results of Ahmed glaucoma valve and Molteno implant in neovascular glaucoma. Eye. 2007;21(1):65–70.
24. Sisto D, et al. The role of antimetabolites in filtration surgery for neovascular glaucoma: intermediate-term follow-up. Acta Ophthalmol Scand. 2007;85(3):267–71.
25. Flanagan DW, Blach RK. Place of panretinal photocoagulation and trabeculectomy in the management of neovascular glaucoma. Br J Ophthalmol. 1983;67(8):526–8.
26. Clearkin LG. Recent experience in the management of neovascular glaucoma by pan-retinal photocoagulation and trabeculectomy. Eye. 1987;1(Pt 3):397–400.
27. Kiuchi Y, et al. Trabeculectomy with mitomycin C for treatment of neovascular glaucoma in diabetic patients. Ophthalmologica. 2006;220(6):383–8.
28. Hong CH, et al. Glaucoma drainage devices: a systematic literature review and current controversies. Surv Ophthalmol. 2005;50(1):48–60.
29. Mandal AK, et al. Mitomycin-C-augmented trabeculectomy for neovascular glaucoma. A preliminary report. Indian J Ophthalmol. 2002;50(4):287–93.
30. Euswas A, Warrasak S. Long-term results of early trabeculectomy with mitomycin-C and subsequent posterior segment intervention in the treatment of neovascular glaucoma with hazy ocular media. J Med Assoc Thai. 2005;88(11):1582–90.
31. Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. Retina. 2006;26(3):352–4.
32. Avery RL, et al. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. Ophthalmology. 2006;113(10):1695.e1–15.
33. Chilov MN, Grigg JR, Playfair TJ. Bevacizumab (Avastin) for the treatment of neovascular glaucoma. Clin Experiment Ophthalmol. 2007;35(5):494–6.
34. Gheith ME, et al. Role of intravitreal bevacizumab in neovascular glaucoma. J Ocul Pharmacol Ther. 2007;23(5):487–91.
35. Grisanti S, et al. Intracameral bevacizumab for iris rubeosis. Am J Ophthalmol. 2006;142(1):158–60.
36. Iliev ME, et al. Intravitreal bevacizumab (Avastin) in the treatment of neovascular glaucoma. Am J Ophthalmol. 2006;142(6):1054–6.
37. Kelkar AS, et al. The use of intravitreal bevacizumab in neovascular glaucoma: a case report. Bull Soc Belge Ophtalmol. 2007;303:43–5.
38. Mason III JO, et al. Regression of neovascular iris vessels by intravitreal injection of bevacizumab. Retina. 2006;26(7):839–41.
39. Oshima Y, et al. Regression of iris neovascularization after intravitreal injection of bevacizumab in patients with proliferative diabetic retinopathy. Am J Ophthalmol. 2006;142(1):155–8.
40. Silva Paula J, et al. Short-term results of intravitreal bevacizumab (Avastin) on anterior segment neovascularization in neovascular glaucoma. Acta Ophthalmol Scand. 2006;84(4):556–7.
41. Vatavuk Z, Bencic G, Mandic Z. Intravitreal bevacizumab for neovascular glaucoma following central retinal artery occlusion. Eur J Ophthalmol. 2007; 17(2):269–71.
42. Yazdani S, Hendi K, Pakravan M. Intravitreal bevacizumab (Avastin) injection for neovascular glaucoma. J Glaucoma. 2007;16(5):437–9.
43. Elmekawey H, Khafagy A. Intracameral ranibizumab and subsequent mitomycin C augmented trabeculectomy in neovascular glaucoma. J Glaucoma. 2014; 23(7):437–40.
44. Luke J, et al. Ranibizumab as adjuvant in the treatment of rubeosis iridis and neovascular glaucoma—results from a prospective interventional case series. Graefes Arch Clin Exp Ophthalmol. 2013; 251(10):2403–13.
45. Altintas AG, et al. Effect on anterior chamber bevacizumab injection combined with seton implantation in treatment of rubeosis iridis in neovascular glaucoma. Cutan Ocul Toxicol. 2012;31(2):124–7.
46. Miki A, et al. One-year results of intravitreal bevacizumab as an adjunct to trabeculectomy for neovascular glaucoma in eyes with previous vitrectomy. Eye (Lond). 2011;25(5):658–9.
47. Ma KT, et al. Surgical results of Ahmed valve implantation with intraoperative bevacizumab injection in patients with neovascular glaucoma. J Glaucoma. 2012;21(5):331–6.

48. Takihara Y, et al. Combined intravitreal bevacizumab and trabeculectomy with mitomycin C versus trabeculectomy with mitomycin C alone for neovascular glaucoma. J Glaucoma. 2011;20(3):196–201.
49. Arcieri ES, et al. Efficacy and safety of intravitreal bevacizumab in eyes with neovascular glaucoma undergoing Ahmed glaucoma valve implantation: 2-year follow-up. Acta Ophthalmol. 2015;93(1): e1–6.
50. Mahdy RA, et al. Efficacy of intravitreal bevacizumab with panretinal photocoagulation followed by Ahmed valve implantation in neovascular glaucoma. J Glaucoma. 2013;22(9):768–72.
51. Higashide T, et al. Adverse events associated with intraocular injections of bevacizumab in eyes with neovascular glaucoma. Graefes Arch Clin Exp Ophthalmol. 2012;250(4):603–10.
52. Ryoo NK, Lee EJ, Kim TW. Regression of iris neovascularization after subconjunctival injection of bevacizumab. Korean J Ophthalmol. 2013;27(4): 299–303.
53. Waisbourd M, et al. Topical bevacizumab for neovascular glaucoma: a pilot study. Pharmacology. 2014;93(3–4):108–12.
54. Hollands H, et al. Short-term intraocular pressure changes after intravitreal injection of bevacizumab. Can J Ophthalmol. 2007;42(6):807–11.
55. Rosenfeld PJ, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1419–31.
56. Brown DM, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432–44.
57. Good TJ, et al. Sustained elevation of intraocular pressure after intravitreal injections of anti-VEGF agents. Br J Ophthalmol. 2011;95(8):1111–4.
58. Jalil A, Fenerty C, Charles S. Intravitreal bevacizumab (Avastin) causing acute glaucoma: an unreported complication. Eye. 2007;21(12):1541.
59. Skalicky SE, et al. Glaucoma filtration surgery following sustained elevation of intraocular pressure secondary to intravitreal anti-VEGF injections. Ophthalmic Surg Lasers Imaging. 2012;43(4):328–34.
60. Bakri SJ, et al. Intraocular pressure in eyes receiving monthly ranibizumab in 2 pivotal age-related macular degeneration clinical trials. Ophthalmology. 2014; 121(5):1102–8.
61. Kim YJ, et al. Long-term effects of multiple intravitreal antivascular endothelial growth factor injections on intraocular pressure. Am J Ophthalmol. 2014; 157(6):1266–71.e1.
62. Susanna Jr R. Partial Tenon's capsule resection with adjunctive mitomycin C in Ahmed glaucoma valve implant surgery. Br J Ophthalmol. 2003;87(8): 994–8.
63. Krupin T, et al. Long-term results of valve implants in filtering surgery for eyes with neovascular glaucoma. Am J Ophthalmol. 1983;95(6):775–82.
64. Minckler DS, et al. Clinical experience with the single-plate Molteno implant in complicated glaucomas. Ophthalmology. 1988;95(9):1181–8.
65. Lloyd MA, et al. Clinical experience with the single-plate Molteno implant in complicated glaucomas. Update of a pilot study. Ophthalmology. 1992;99(5):679–87.
66. Downes RN, et al. The Molteno implant in intractable glaucoma. Eye. 1988;2(Pt 3):250–9.
67. Freedman J, Rubin B. Molteno implants as a treatment for refractory glaucoma in black patients. Arch Ophthalmol. 1991;109(10):1417–20.
68. Ancker E, Molteno AC. Molteno drainage implant for neovascular glaucoma. Trans Ophthalmol Soc U K. 1982;102(Pt 1):122–4.
69. Faghihi H, et al. Pars plana Ahmed valve implant and vitrectomy in the management of neovascular glaucoma. Ophthalmic Surg Lasers Imaging. 2007;38(4):292–300.
70. Chalam KV, et al. Pars plana modified Baerveldt implant versus neodymium:YAG cyclophotocoagulation in the management of neovascular glaucoma. Ophthalmic Surg Lasers. 2002;33(5):383–93.
71. Herschler J, Agness D. A modified filtering operation for neovascular glaucoma. Arch Ophthalmol. 1979;97(12):2339–41.
72. Lee PF, Shihab ZM, Fu YA. Modified trabeculectomy: a new procedure for neovascular glaucoma. Ophthalmic Surg. 1980;11(3):181–5.
73. Fernandez-Vigo J, et al. Treatment of diabetic neovascular glaucoma by panretinal ablation and trabeculectomy. Acta Ophthalmol (Copenh). 1988;66(6): 612–6.
74. Kiuchi Y, et al. Pars plana vitrectomy and panretinal photocoagulation combined with trabeculectomy for successful treatment of neovascular glaucoma. Graefes Arch Clin Exp Ophthalmol. 2006;244(12): 1627–32.
75. Kono T, et al. Long-term results of pars plana vitrectomy combined with filtering surgery for neovascular glaucoma. Ophthalmic Surg Lasers Imaging. 2005; 36(3):211–6.

Pediatric Glaucoma: IOP, Axial Length, and Surgery Indications

50

JoAnn A. Giaconi and Anne L. Coleman

Core Messages

- Children are not small adults; the outcomes of pediatric glaucoma and surgery are dependent on age, as well as on the type and severity of glaucoma.
- Intraocular pressure (IOP) measurements in the pediatric population are affected by sedation, mode of airway securement, tonometer being used, central corneal thickness (CCT), and corneal hysteresis.
- In children, CCT and hysteresis vary with age and glaucoma diagnosis.
- Many tonometers have been shown to estimate IOP inaccurately in children.
- Axial length is an important parameter to follow in young children with glaucoma.

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50.1 What Is the Best Way to Measure IOP in the Pediatric Patient?

If possible, it is best to measure intraocular pressure (IOP) in a cooperative, alert, and wakeful child. Many different variables can affect IOP measurement in the pediatric age group. These include cooperation (if measuring IOP in the clinic), anesthetic agents and the mode of airway securement (if measuring IOP during examination under anesthesia (EUA)), the tonometer being used, central corneal thickness (CCT), and corneal hysteresis. The great variability and interplay between these factors make it difficult to know if one is truly obtaining an accurate measure of the IOP. This uncertainty is why clinical experience can be vital and why other findings—the optic nerve exam, corneal diameter, and axial length—should be weighed more heavily than IOP when making judgments as to whether a child's glaucoma is stable or progressing. The following paragraphs provide evidence-based facts as to how these variables may affect IOP, in order to help you interpret IOP readings in children.

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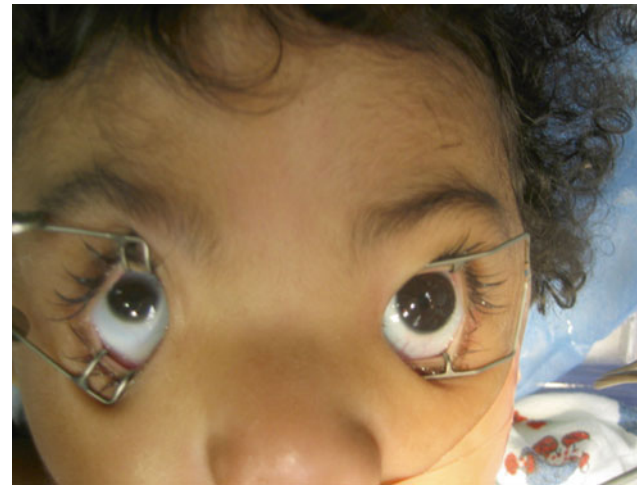

Fig. 50.1 Child with microophthalmia OD and glaucoma suspect OS who is undergoing EUA. Speculums to separate the eyelids may falsely elevate IOP

50.1.1 What Factors in Pediatric Examination Elevate and Reduce IOP?

If a child struggles against the examination, they will perform valsalva maneuvers. Valsalva maneuvers can raise IOP, making it technically impossible to obtain an accurate measurement [1, 2]. Often, a clinician resorts to an EUA or sedation to obtain better measurements and better examination of the eye. In cases of general anesthesia, to obtain the IOP truest to that found in the wakeful state, IOP should be measured as soon as possible following induction of anesthesia [3].

With sedation and anesthesia, there exists the possibility that these medications will alter IOP from its original level. Oral *chloral hydrate* is a hypnotic sedative that has been used for conscious sedation. It was found not to alter IOP measurements in a small series of normal and glaucomatous eyes [4]. However, many US clinics and hospitals no longer allow chloral hydrate's use without active monitoring, since respiratory arrest is possible. *Midazolam* is an anxiolytic that can be used as a preoperative sedative, and which has been shown not to alter IOP in adults [5]. Most *general anesthetics* lower IOP by variable amounts and at variable times after administration. In one study comparing sevoflurane (an inhalational agent that has largely replaced its older counterpart halothane) to ketamine (a dissociative anesthetic that is injected intramuscularly), sevoflurane significantly lowered IOP 2–8 min after the initial IOP measurement. IOP continued to fall as time passed and the mean IOP decrease was as much as 19 %. In the ketamine group, IOP did not change between the first possible measurement and measurements taken over the next 8 min [3]. Reports on *ketamine* have varied, with some showing that it significantly elevates IOP [6], whereas others show it to have a very modest IOP effect [7, 8].

Another issue during EUA can be speculum use, which can raise IOP [9] (Fig. 50.1). The method of *securing the airway* has been studied and found to have an effect on IOP, as well. Tracheal intubation can raise IOP by a few points compared to laryngeal mask airways, which cause no change in IOP [10, 11]. At UCLA, our practice during EUA is to premedicate patients with oral midazolam and then to perform a mask inhalational induction with oxygen, nitrous oxide, and sevoflurane. The IOP is measured before the airway is manipulated using a pneumatonometer.

50.1.2 How Do Central Corneal Thickness and Hysteresis Affect IOP Measurement in Children?

CCT and biomechanical properties of the cornea, such as corneal *hysteresis*, affect IOP measurement readings. Once the pediatric eye reaches

adult status, corneal effects on IOP readings are similar to what we see in adults. The normal pediatric cornea reaches adult thickness between 2 and 4 years of age [12]. Racial differences in the thickness of normal pediatric corneas have been found, just as seen in adults. A study out of Duke University in the United States reported that the mean CCT of Black children was significantly thinner than that of White children (543 ± 27 vs. 562 ± 35 μm) [13]. In children with glaucoma, CCT varies by disease stage and type of glaucoma. In primary congenital glaucoma, CCT is thinner (excluding scarred corneas) compared with age-matched controls [14]. Corneas are thinner with more severe congenital glaucoma [15]. A strong negative correlation exists between corneal diameter and CCT [14, 16]. This fact is due to thinning of the cornea as it is stretched under high IOPs. In addition, CCT can vary depending on where in the evolution of congenital glaucoma the eye stands. In the acute phase with elevated IOP, the cornea may be thick with edema. One study concluded that even apparently clear corneas under high IOP in congenital glaucoma might have subclinical edema, as they found CCT to be thicker preoperatively compared to 2 weeks later following trabeculectomy [17]. CCT also depends on the specific diagnosis of glaucoma. In secondary pediatric glaucomas, such as aphakic, Axenfeld-Rieger, Sturge-Weber, or aniridic glaucoma, much thicker CCTs have been found in comparison to CCT in primary congenital glaucoma [16, 18].

There are few studies on pediatric corneal biomechanical properties. One study of pediatric corneal hysteresis (42 normal kids, aged 4–18 years of age) shows that corneal hysteresis in normal children (mean value 12.5 mmHg) matches adult hysteresis. However, the hysteresis of corneas in children with congenital glaucoma is greatly reduced (mean value 6.3 mmHg) and was lowest in the largest diameter corneas [19].

Summary for the Clinician

- IOP in the awake state is the "gold standard".
- During EUA, anesthetic agents, speculums, and mode of airway securement can all affect the IOP reading; the IOP measured as soon as possible following induction is best.
- There is a negative correlation between corneal diameter and central corneal thickness in congenital glaucoma.
- In pediatric glaucomas other than primary congenital glaucoma, the central corneal thickness tends to be thicker.
- Hysteresis is reduced in congenital glaucoma and tends to be lowest in those with the greatest corneal diameter.

50.2 Is One Instrument Better Than Another for Measuring IOP in the Pediatric Age Group?

Pneumatonometry may be the best method of measuring IOP in the pediatric age group. Applanation tonometry IOP estimations in young children were found to be well below average adult values, but caught up to adult values with increasing age and were equivalent to adult values by the age of 10. The underestimation of IOP by applanation in young children may be the result of different biomechanical properties in infant eyes. Biomechanical properties are appreciated as having a large effect on IOP estimates by various instruments. In a study on children and adults undergoing ocular surgery, pneumatonometry provided the closest estimation of true IOP, set manometrically via an infusion cannula to low, medium, and high levels. Pneumatonometry estimates of IOP did not appear to be affected by age. There was a significant difference in the estimate of IOP by Perkins applanation and pneumatonometry, with pneumatonometry estimates being much closer to true IOP than applanation or even TonoPen estimates. It must be noted that pneumatonometry did overestimate at low IOPs and slightly underestimated at high IOPs (less than

0.5 mmHg over 21.9 mmHg) and so was not perfect [20].

The accuracy of the various *TonoPen* tonometers is controversial. Numerous studies have found that TonoPens significantly underestimate IOP compared to Goldmann applanation or manometrically determined pressure [20–22]. One study reported a mean difference of −4.2 mmHg between the Goldmann and TonoPen instruments when IOP was greater than 20 mmHg (on Goldmann measurement) with a large 95 % confidence interval of −13.2 to 4.8 mmHg [23, 24]. This large potential underestimation of IOP (as much as 13 mmHg) is a concern when monitoring the IOP control of a child with glaucoma. The Schiötz tonometer overestimates IOP compared to the TonoPen or Perkins tonometer [25].

The *Ocular Response Analyzer*, which directs a jet of air toward the cornea to obtain measurements, has also been studied in a pediatric age group. Its purported advantage is that it is less affected by CCT and can measure corneal hysteresis. Better cooperation was reported with IOP measurements with this instrument, but the instrument does require fixation upon a target light and so it may not be useful in very young children, those with nystagmus, or during EUA [19]. The IOP measurements were reported not to differ from Goldmann applanation measurements.

Rebound tonometry has become popular in pediatric clinics because it is hand-held and requires no anesthetic to obtain a measurement. It has decreased the need for EUAs because it is easier to obtain IOP measurements in awake children [26]. However, there are a number of studies showing that rebound tonometry gives higher readings than Goldmann applanation (higher in 75 % of readings although most readings are within 3 mmHg) and that the magnitude of higher readings depends on the level of IOP and CCT. Readings greater than 10 mmHg higher than Goldmann applanation were not uncommon. The recommendation is that if a rebound tonometry reading is in the "normal" range the values are likely correct, but if the reading is high another method of IOP measurement should be sought before going to EUA and the physician needs to interpret readings within context [27, 28].

For a more extensive discussion of instruments to measure IOP, one may refer to Chap. 9.

Summary for the Clinician

- Pneumatonometry may be the best method for measuring IOP in pediatric glaucomas—it is less affected by age than other methods.
- Mean applanation IOP in children is lower than that in adults, but by the age of 10 they are equivalent.
- Tonopen measurements can greatly underestimate IOP when Goldmann IOP is high (>20 mmHg).
- Rebound tonometry overestimates IOP with higher discrepancy from Goldmann applanation at high IOP levels. However, it is very convenient in young children.

50.3 How Is Axial Length Measurement Used in Pediatric Glaucoma?

A child's globe is distensible due to softer and more elastic collagen fibers under the age of 3 years [29]. The eye may be significantly stretched if IOP is highly elevated. This distensibility allows significant increases in corneal diameter and axial length in congenital glaucoma where IOP is typically 30–40 mmHg. Studies have shown that in many eyes with congenital glaucoma, axial lengths are longer than what is expected for age [30–32]. If IOP remains uncontrolled after surgical intervention, axial length will continue to increase [33]. Therefore, serial axial length measurements may be used to monitor the status of eyes with congenital glaucoma. If axial growth is accelerated as compared to the normal pediatric growth curve (see Fig. 50.2), whether or not IOP is elevated, this is a strong indication for a repeat surgery. A "normal" or "low" IOP measurement may be the result of the use of anesthesia, giving the surgeon a false sense of security.

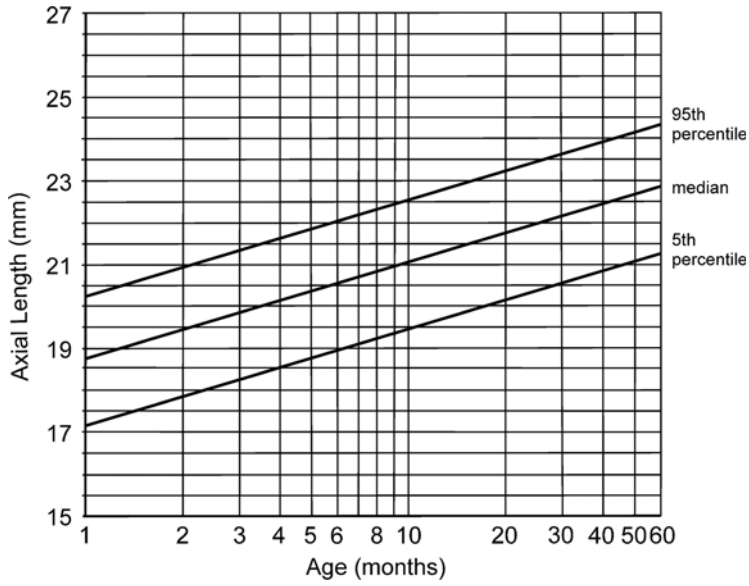

Fig. 50.2 Axial length growth chart used by the Stein Eye glaucoma division for young children with glaucoma. The *y*-axis represents axial length and the *x*-axis represents age in months. The area between the *upper* and *lower lighter lines* represents the normal range of axial length at each age. The *middle, darker line* represents average axial length of normal eyes. If a child's axial length begins within the area bounded by the lines but then grows so that it is outside of the normal range, this represents abnormal growth of the distensible pediatric eye due to elevated IOP

A few pearls to keep in mind. Younger children have more distensible globes than older children. In eyes where glaucoma starts after the age of 4 years, axial length may be a much less important follow-up parameter, as little if any distension of the sclera is expected to occur. Eyes with congenital glaucoma have less myopia than would be expected for their increased axial length because other parts of the eye are affected in a way that compensates for the increased axial length. The cornea and axial lens diameter flatten and the anterior chamber deepens. Axial length has been found to be a more precise parameter of eye growth than corneal diameter [31, 32], except in one study [34].

Summary for the Clinician

- Younger children have more distensible globes.
- Axial length is used to monitor progression of glaucoma up to age 3–4 years. It is helpful, given that IOP measurement is not always accurate in this age group.
- Axial length may be a more precise measurement of eye growth than corneal diameter.

50.4 When Should Surgery Be Performed in Congenital Glaucoma, in Juvenile-Onset Glaucoma, and in Secondary Type Pediatric Glaucomas? What Factors Help Me Decide Which Procedure to Perform?

Primary congenital glaucoma almost always is managed surgically. Due to an abnormal angle, this glaucoma does not respond adequately to medical therapy and angle surgery is required as soon as it can be performed. If the cornea is clear,

surgery can be performed via an internal approach or goniotomy. In *goniotomy*, angle tissue is incised with a goniotomy knife or needle with the aid of a goniolens. If the cornea is edematous or scarred, precluding a gonioscopic view of the angle, then ab externo trabeculotomy should be performed (see Chap. 52 for goniotomy techniques). In *trabeculotomy,* Schlemm's canal is identified by external dissection, and the trabecular meshwork is incised by passing a probe into the canal and rotating it into the anterior chamber (see Chap. 52 for trabeculotomy techniques). It has been reported that Schlemm's canal cannot be located in 11–15 % of cases [35], so one must be prepared with an alternative plan if trabeculotomy cannot be performed successfully. Angle surgery success rates of 75–90 % are reported in retrospective studies from Western societies and 54–69 % in Middle Eastern and South Asian countries [36]. If and when primary angle surgery fails in this group of glaucomas, one is faced with a choice of trabeculectomy with or without antimetabolite, glaucoma drainage device (GDD) surgery, or cyclodestructive procedures, which are discussed below. It is important to note that congenital glaucoma is a high pressure glaucoma, and because there may not be severe, irreversible optic nerve damage yet, IOP reduction to the low to mid 20s may result in a stable clinical course [37].

In secondary pediatric glaucomas, such as aphakic/pseudophakic glaucoma, glaucomas associated with developmental anomalies (i.e., Peters anomaly), or glaucomas associated with phakomatoses, primary angle surgery may not be indicated. After medical failure, these eyes may do better with trabeculectomy, GDD, or cyclodestruction. Juvenile glaucoma has a later onset, after the angle has matured. In these children, medical management should be attempted initially. The decision to proceed with surgery will depend on the failure of medical therapy after weighing the risks and benefits of surgery at that particular time.

It is important to note that there are no large prospective studies comparing the surgical options in children, namely because pediatric glaucoma is a diverse and relatively rare disease with a wide variation in treatment patterns depending on experience and center. Also of importance is that definitions of success vary from study to study; what is considered successful in a published report may be an acceptable yet somewhat disappointing outcome in the clinic. Reported success rates at 1 year for *trabeculectomy* in children are lower than those reported in adults [36]. Use of 5-fluorouracil and mitomycin-C (MMC) improves success rates modestly. Successful IOP control appears dependent on the type and severity of glaucoma and age of the patient. Younger patient age is associated with less success. Moderate to severe primary congenital glaucoma is associated with less success [38, 39]. In phakic children older than 1 year of age, trabeculectomy with MMC has been used with moderate success in various forms of pediatric glaucoma [40–42]. In infants with failed angle surgery, aphakia/pseudophakia, and developmental anomalies of the eye, MMC trabeculectomy does not appear to provide IOP control of sufficient duration due to tissue scarring. In cases of successful pediatric blebs, there is a very high rate of bleb-related endophthalmitis. *Glaucoma drainage devices (GDDs)* may offer better IOP control for a longer period of time than do trabeculectomies in very young patients (Fig. 50.3). GDDs also may be more attractive as they require less postoperative manipulation/care, such as digital massage, laser suture lysis, and subconjunctival injection of 5-FU. However, there is a price to be paid for the IOP "success." In a retrospective, age-matched study comparing MMC trabeculectomy to GDD in children less than 2 years of age, the cumulative probability of success was higher in the GDD group in terms of IOP control (defined as IOP < 23 mmHg on maximally tolerated medications)—87 % vs. 36 % successful at 12 months and 53 % vs. 19 % at 72 months. The mean value for preoperative IOP in the GDD group was 32.9 ± 6.5 mmHg on 2.4 medications and at the last follow-up decreased to 20.8 ± 8.6 on 1.1 medications. In the last follow-up, the mean IOP in the MMC trabeculectomy group was 27.3 ± 12.2 mmHg on 1 medication (starting from a similar preop IOP). It is important to note that there was a declining rate of success with increased follow-up in the GDD group, similar to that seen in adults. The GDD group did experience more postoperative complications than the MMC trabeculectomy

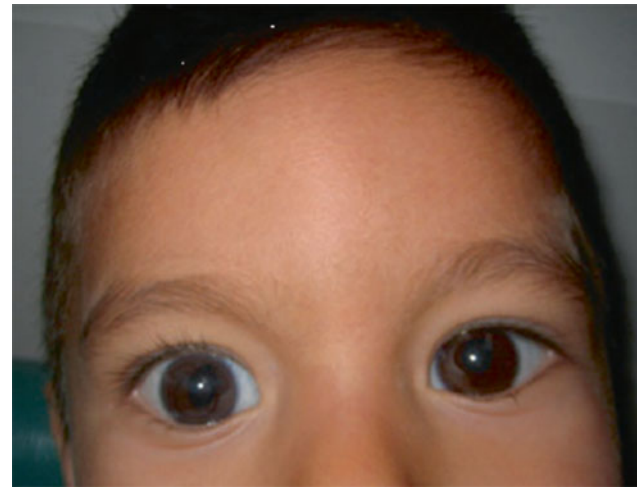

Fig. 50.3 A child with primary congenital glaucoma and buphthalmos who underwent two unsuccessful goniotomies per eye. Subsequent surgery was Ahmed valve placement in each eye. IOP post-GDD has been maintained in the mid-teens for years without medication and optic nerve damage reversed itself

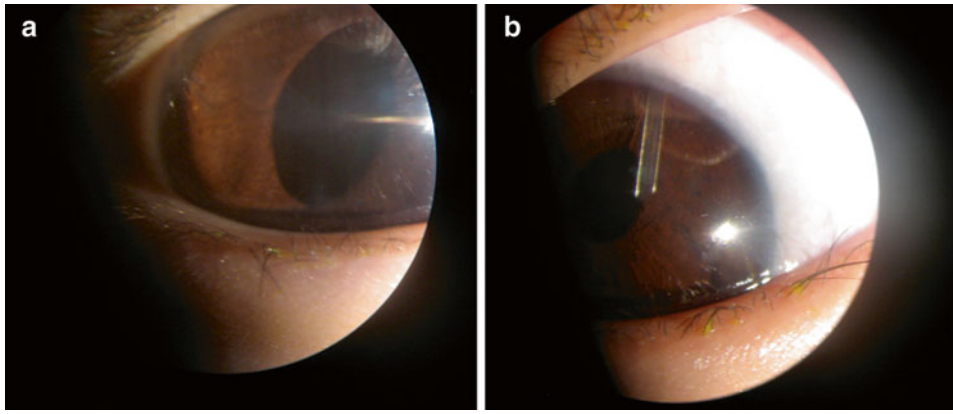

Fig. 50.4 Close-ups of the eyes of patient shown in Fig 50.3. (**a**) The tube in the right eye has retracted somewhat from its original position and is more anteriorly located towards the cornea than when originally placed. (**b**) The anterior chamber segment of tube in the left eye is longer than when it was originally placed. The corneas remain without stromal edema

group, with almost half the patients requiring a trip back to the operating room. The most common procedure performed in one-third of subjects was tube repositioning (Fig. 50.4). Another study of pediatric glaucomas that enrolled an older age group, 6–17 years of age, showed equal results between the Ahmed valve (88 %) and MMC trabeculectomy (86 %) with a median follow-up of 1.5 years (range 0.5–5 years). In Saudi Arabia, the procedure of choice for moderate and severe forms of primary congenital glaucoma is the combined trabeculotomy-trabeculectomy with MMC. Authors have reported that 75 % of their cases ($n=672$) maintained an IOP ≤ 21 mmHg without additional medication or surgery and stable corneal diameters and optic nerves for at least 1 year following surgery [38].

Complications of GDDs are similar to those encountered in adults. However, a child's eye may grow during the first few years of follow-up, which can lead to a high rate of tube-cornea touch (5.7–26.2 %). As the pliable eye grows, the tube may rotate forward towards the cornea. Additional complications particularly reported in children, but not necessarily unique to them, include implant exposure, strabismus, fibrous ingrowth,

and vitreous occlusion if aphakic. Trabeculectomy with adjunctive MMC in the pediatric age group carries a particularly high risk of bleb-related complications, much higher than that reported in adults. Endophthalmitis rates as high as 7–14 % have been noted in pediatric case series [37]. Complications seen with either type of surgery include shallow anterior chambers requiring reformation, corneal decompensation, corneal blood staining, choroidal detachments, choroidal hemorrhage, aqueous misdirection, and cataracts.

Cycloablative procedures have traditionally been reserved for end-stage glaucoma both in adults and children for fear of inducing chronic hypotony after destroying aqueous humor production. Cyclocryotherapy has been reported to have a 44 % success rate after 4 years with a high rate of devastating complications, such as phthisis [43]. Transscleral cyclophotocoagulation (TCP) in end-stage pediatric glaucoma has met study criteria of successful IOP reduction in up to two-thirds of patients after 1 year. To achieve success, multiple treatments are often needed. The ciliary processes in pediatric glaucomas can be displaced from the normal adult location, so that TCP does not always reach the target tissue unless adjustments are made [44–46]. Endoscopic cyclophotocoagulation (ECP) can deliver lower energy more precisely to the ciliary processes via a probe used inside the eye. As with any surgical procedure, patient selection is important. Pediatric endocyclophotocoagulation has been shown to work best in aphakic/pseudophakic patients, although these results are modest. In the largest series ($n = 34$ eyes of 25 patients) with the longest follow-up (mean follow-up 44.4 months) of subjects <16 years of age with aphakic/pseudophakic glaucoma, overall success rate was 53 % (IOP < 24 mmHg and IOP decrease >15 % despite glaucoma medications) with two-thirds of the eyes requiring more than one treatment. Eighty-two percent of the eyes in this series underwent ECP as the primary surgical procedure for glaucoma. An encouraging fact is that of the eight eyes that received 360° of treatment, no postoperative hypotony was encountered. Alvarado estimated that approximately 60 % of the ciliary body tissue area is ablated when treating processes over 360° [47]. In a retrospective review of 12 eyes with Peters anomaly and corneal scarring/failed corneal graft where ECP was generally the second, third, or fourth glaucoma intervention, ECP had very limited success (17 %). Complications reported with pediatric ECP include retinal detachment, chorioretinal detachment, chronic hypotony, hyphema, and loss of vision.

Deciding which surgical intervention to use in an individual child can be a clinical dilemma. Factors to examine are the child's age, type of glaucoma, glaucoma severity, lens status, surgeon experience with procedure and postoperative care, access to frequent EUA, reliability of caretakers, along with the risks and benefits of each individual procedure. With pediatric glaucoma, repeat surgery is generally the rule and lifetime surveillance is necessary. Parents and caretakers should be informed of this upfront so that they have realistic expectations and are not disappointed by the results. The symptoms and signs of complications also must be thoroughly discussed.

Summary for the Clinician

- In primary congenital glaucoma, surgery is the treatment of choice due to an undeveloped outflow pathway.
- Patient selection is extremely important in deciding which procedure to perform in pediatric glaucoma.
- In children <6 years of age, where angle surgery has failed or is not indicated, a glaucoma drainage device may be a better option than trabeculectomy for IOP control.
- There is a very high rate of bleb-related endophthalmitis in pediatric MMC trabeculectomies.
- Repeat surgery in pediatric glaucoma is extremely common and lifetime surveillance is necessary.
- Tube-corneal touch is seen in a high percentage of tubes placed in the pediatric population and may be the result of eye growth in the early years.
- Cycloablative procedures have a role in pediatric glaucomas.

References

1. Dada T, Gupta V, Deepak KK, et al. Narrowing of the anterior chamber angle during valsalva maneuver: a possible mechanism for angle-closure. Eur J Ophthalmol. 2006;16:81–91.
2. Frantz KA, Peters RJ, Maino DM, et al. Effect of resisting tonometry on intraocular pressure. J Am Optom Assoc. 1994;65:732–6.
3. Blumberg D, Congdon N, Jampel H, et al. The effects of sevoflurane and ketamine on intraocular pressure in children during examination under anesthesia. Am J Ophthalmol. 2007;143:494–9.
4. Jaafar MS, Kazi GA. Effect of oral chloral hydrate sedation on the intraocular pressure measurement. J Pediatr Ophthalmol Strabismus. 1993;30:372–6.
5. Carter K, Faberowski LK, Sherwood MB, et al. A randomized trial of the effect of midazolam on intraocular pressure. J Glaucoma. 1999;8:204–7.
6. Yoshikawa K, Murai Y. The effect of ketamine on intraocular pressure in children. Anesth Analg. 1971;50:199–202.
7. Ausinsch B, Rayburn RL, Munson ES, et al. Ketamine and intraocular pressure in children. Anesth Analg. 1976;55:773–5.
8. Peuler M, Glass DD, Arens JF. Ketamine and intraocular pressure. Anesthesiology. 1975;43:575–8.
9. Epley KD, Tychsen L, Lueder GT. The effect of an eyelid speculum on intraocular pressure measurement in children. Am J Ophthalmol. 2002;134:926–7.
10. Duman A, Ogun CO, Okesli S. The effect on intraocular pressure of tracheal intubation or laryngeal mask insertion during sevoflurane anaesthesia in children without the use of muscle relaxants. Paediatr Anaesth. 2001;11:421–4.
11. Tangwiwat S, Kumphong P, Surasaraneewong S, et al. Intraocular pressure changes during general anesthesia in children, comparing no mask, undermask and laryngeal mask airway. J Med Assoc Thai. 2002;85 Suppl 3:S975–9.
12. Ehlers N, Sorensen T, Bramsen T, et al. Central corneal thickness in newborns and children. Acta Ophthalmol (Copenh). 1976;54:285–90.
13. Muir KW, Duncan L, Enyedi LB, et al. Central corneal thickness in children: racial differences (black vs. white) and correlation with measured intraocular pressure. J Glaucoma. 2006;15:520–3.
14. Henriques MJ, Vessani RM, Reis FA, et al. Corneal thickness in congenital glaucoma. J Glaucoma. 2004;13:185–8.
15. Wygnanski-Jaffe T, Barequet IS. Central corneal thickness in congenital glaucoma. Cornea. 2006;25:923–5.
16. Tai TY, Mills MD, Beck AD, et al. Central corneal thickness and corneal diameter in patients with childhood glaucoma. J Glaucoma. 2006;15:524–8.
17. Oberacher-Velten I, Prasser C, Lorenz B. Evolution of central corneal thickness in children with congenital glaucoma requiring glaucoma surgery. Graefes Arch Clin Exp Ophthalmol. 2008;246(3):397–403.
18. Lopes JE, Wilson RR, Alvim HS, et al. Central corneal thickness in pediatric glaucoma. J Pediatr Ophthalmol Strabismus. 2007;44:112–7.
19. Kirwan C, O'Keefe M. Corneal hysteresis using the Reichert ocular response analyser: findings pre- and post-LASIK and LASEK. Acta Ophthalmol. 2008;86(2):215–8.
20. Eisenberg DL, Sherman BG, McKeown CA, et al. Tonometry in adults and children. A manometric evaluation of pneumatonometry, applanation, and tonopen in vitro and in vivo. Ophthalmology. 1998;105:1173–81.
21. Broman AT, Congdon NG, Bandeen-Roche K, et al. Influence of corneal structure, corneal responsiveness, and other ocular parameters on tonometric measurement of intraocular pressure. J Glaucoma. 2007;16:581–8.
22. Iester M, Mermoud A, Achache F, et al. New tonopen XL: comparison with the Goldmann tonometer. Eye. 2001;15:52–8.
23. Horowitz GS, Byles J, Lee J, et al. Comparison of the tono-pen and Goldmann tonometer for measuring intraocular pressure in patients with glaucoma. Clin Experiment Ophthalmol. 2004;32:584–9.
24. Levy J, Lifshitz T, Rosen S, et al. Is the tono-pen accurate for measuring intraocular pressure in young children with congenital glaucoma? J AAPOS. 2005;9:321–5.
25. Bordon AF, Katsumi O, Hirose T. Tonometry in pediatric patients: a comparative study among Tono-pen, Perkins, and Schiotz tonometers. J Pediatr Ophthalmol Strabismus. 1995;32:373–7.
26. Grigman F, Grigman AP, Olitsky SE. The use of the iCare tonometer reduced the need for anesthesia to measure IOP in children. J AAPOS. 2012;16:508–10.
27. Dahlmann-Noor AH, Puertas R, Tabasa-Lim S, et al. Comparison of handheld rebound tonometry with Goldmann applanation tonometry in children with glaucoma: a cohort study. BMJ Open. 2013;3:e001788. doi:10.1136/bmjopen-2012-001788.
28. Flemmons MS, Hsaio YC, Dzau J, et al. iCare rebound tonometry in children with known and suspected glaucoma. J AAPOS. 2013;15:153–7.
29. Dickens CJ, Hoskins HD. Diagnosis and treatment of congential glaucoma. In: Ritch R, Shields MB, Krupin T, editors. The glaucoma: clinical science. 2nd ed. St Louis: Mosby; 1996. p. 739–49.
30. Law SK, Bui D, Caprioli J. Serial axial length measurements in congenital glaucoma. Am J Ophthalmol. 2001;132:926–8.
31. Sampaolesi R, Caruso R. Ocular echometry in the diagnosis of congenital glaucoma. Arch Ophthalmol. 1982;100:574–7.
32. Tarkkanen A, Uusitalo R, Mianowicz J. Ultrasonographic biometry in congenital glaucoma. Acta Ophthalmol (Copenh). 1983;61:618–23.

33. Kiefer G, Schwenn O, Grehn F. Correlation of postoperative axial length growth and intraocular pressure in congenital glaucoma – a retrospective study in trabeculotomy and goniotomy. Graefes Arch Clin Exp Ophthalmol. 2001;239:893–9.
34. Kiskis AA, Markowitz SN, Morin JD. Corneal diameter and axial length in congenital glaucoma. Can J Ophthalmol. 1985;20:93–7.
35. Elder MJ. Congenital glaucoma in the West Bank and Gaza Strip. Br J Ophthalmol. 1993;77:413–6.
36. Tanimoto SA, Brandt JD. Options in pediatric glaucoma after angle surgery has failed. Curr Opin Ophthalmol. 2006;17:132–7.
37. Beck AD, Freedman S, Kammer J, et al. Aqueous shunt devices compared with trabeculectomy with mitomycin-C for children in the first two years of life. Am J Ophthalmol. 2003;136:994–1000.
38. Al-Hazmi A, Awad A, Zwaan J, et al. Correlation between surgical success rate and severity of congenital glaucoma. Br J Ophthalmol. 2005;89:449–53.
39. Ehrlich R, Snir M, Lusky M, et al. Augmented trabeculectomy in paediatric glaucoma. Br J Ophthalmol. 2005;89:165–8.
40. Al-Hazmi A, Zwaan J, Awad A, et al. Effectiveness and complications of mitomycin C use during pediatric glaucoma surgery. Ophthalmology. 1998;105:1915–20.
41. Beck AD, Wilson WR, Lynch MG, et al. Trabeculectomy with adjunctive mitomycin C in pediatric glaucoma. Am J Ophthalmol. 1998;126:648–57.
42. Mandal AK, Walton DS, John T, et al. Mitomycin C-augmented trabeculectomy in refractory congenital glaucoma. Ophthalmology. 1997;104:996–1001.
43. Wagle NS, Freedman SF, Buckley EG, et al. Long-term outcome of cyclocryotherapy for refractory pediatric glaucoma. Ophthalmology. 1998;105:1921–6.
44. Bock CJ, Freedman SF, Buckley EG, et al. Transscleral diode laser cyclophotocoagulation for refractory pediatric glaucomas. J Pediatr Ophthalmol Strabismus. 1997;34:235–9.
45. Autrata R, Rehurek J. Long-term results of transscleral cyclophotocoagulation in refractory pediatric glaucoma patients. Ophthalmologica. 2003;217:393–400.
46. Kirwan JF, Shah P, Khaw PT. Diode laser cyclophotocoagulation: role in the management of refractory pediatric glaucomas. Ophthalmology. 2002;109:316–23.
47. Alvarado JA. Endocyclophotocoagulation for pediatric glaucoma: a tale of two cities. J AAPOS. 2007;11:10–1.

Pediatric Glaucoma: Glaucoma Medications and Steroids

51

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Core Messages

- Adverse effects of medications can vary depending on the age and weight of a child; some medications can have life-threatening side effects in young children.
- Children can manifest side effects in different ways than do adults.
- Beta blockers and carbonic anhydrase inhibitors are useful topical medications in children.
- Alpha agonists should be avoided in children under 2 years of age.
- Prostaglandin analogs are less useful in younger children.
- Miotics may not be effective in glaucomas with angle dysgenesis.
- The ocular hypertensive response with steroids can be more severe with a quicker time of onset in children, particularly in younger children.

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51.1 Are Adult Doses of Topical Glaucoma Medications Safe in Children?

The majority of medications used for IOP-lowering in adults are not licensed for use in children. Package inserts on topical medications warn that "safety and efficacy has not been established in children." Despite this fact, most topical drops are used in children and are safe. Definitive trials to establish their safety and efficacy are unlikely to occur due to medicolegal constraints, namely, the difficulty in establishing accurate outcome measurements, limited sample sizes, and low financial incentives to drug companies evaluating products in the pediatric population [1].

Prescribers must take into account the age and medical histories of their pediatric patients. Children are at greater risk for systemic side effects because ocular dosing is not weight-adjusted and children may metabolize medications differently than do adults. A newborn is estimated to require 50 % of the adult dosage to obtain the same ocular concentration. This requirement increases to 60 % at 3 years and to 90 % at 6 years of age [2]. Approximately 80 % of each eye drop passes through the nasolacrimal system where it may be rapidly absorbed into the systemic circulation via the nasal mucosa [3]. The blood volume of children, and especially of neonates, is significantly smaller than that of an

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adult, which can lead to significantly higher blood concentrations. For example, blood levels of timolol in five small children ranged from 3.5 to 34.0 ng/ml compared to no more than 2.45 ng/ml in adults, while plasma brimonidine levels in a 1-month-old infant measured 1459 pg/ml after topical instillation in comparison to a maximum of 60 pg/ml in adult studies [4–6]. Neonates also have immature enzyme pathways that may change the elimination half-life of drugs, potentiating side effects [7]. It is extremely important to always educate the caretakers of children as to the signs and symptoms of drug side effects, as small children cannot verbalize what they are experiencing.

51.2 Which Medications Are Typically Used as First-Line Agents in Children?

When medical therapy is required in children, beta blockers and carbonic anhydrase inhibitors (CAIs) have generally been used as first-line agents. Usually, betaxolol (a β_1-selective drug) 0.25 % or timolol 0.25 % (as opposed to 0.5 %) twice daily is used as initial beta-blocker therapy by many specialists in the U.S. In other countries, timolol 0.1 % gel once daily is popular for children because the gel formula is less likely to be systemically absorbed and only one daily dose is necessary. Topical CAIs are generally used two to three times daily at the commercially available concentrations; this more frequent dosing schedule makes them somewhat less desirable as the first-line agent in children. However, of note, a review of medical treatment of pediatric glaucomas in the United Kingdom found prostaglandin analogs to be the most frequently prescribed medication in children there [8].

51.3 What Cautions Are There with Beta Blockers in Children?

With beta blockers, respiratory distress caused by apnea or bronchospasm (β-2 mediated) and bradycardia are major concerns. Small infants and children with asthma are particularly at risk. It may be prudent to avoid beta blockers altogether in premature and small infants. In children, coughing may often be the presenting sign of bronchospasm, as opposed to wheezing in adults. Other side effects are hypotension (β-1 mediated), bradycardia (β-1 mediated), light-headedness, depression, and masked hypoglycemia in diabetic children [1]. Children can also experience local side effects such as ocular stinging, burning, pain, itching, erythema, dry eye, allergic reactions, and occasionally corneal disorders [7].

51.4 What Cautions Are There with Carbonic Anhydrase Inhibitors in Children?

Topical and systemic CAIs have been used for many years in children. Topical treatment is well-tolerated and may have a greater IOP-lowering effect than seen in adults [9].

Systemic therapy produces a greater IOP reduction than topical administration. If systemic CAI is necessary, an effective dose of acetazolamide is 10–20 mg/kg/day (maximum 750 mg daily) divided in two to four doses for children aged 1 month to 12 years, adjusted for response. For children who are 12–18 years old, the recommended dosage is 0.5–1 g daily in two to four divided doses, again adjusted for response [7]. Systemic treatment can be well-tolerated; however, it is generally used as a last choice in attempts to delay or avoid surgery. Side effects to watch for are metabolic acidosis. Poor feeding or weight loss can be a sign of metabolic acidosis in infants [10]. Metabolic acidosis has even been reported in one neonate using topical dorzolamide [10]. Chronic oral acetazolamide has been used in children with epilepsy and was associated with growth retardation, which was attributed to the induced renal metabolic acidosis [11]. Other side effects of CAIs are similar to those found in adults (hypersensitivity reactions, headache, dizziness, paresthesia, sinusitis, rhinitis, nausea, bitter taste, urolithiais, aplastic anemia, and with topical administration: burning, stinging, blurred vision, lacrimation, conjunctivitis, superficial

punctuate keratitis, eyelid inflammation, transient myopia). As with adults, these medications should not be used if a patient has certain metabolic problems (such as hypokalemia or hyponatremia) or if there is severe renal or hepatic impairment (see Chap. 26 for full discussion).

51.5 What Cautions Are There with Topical α-Blockers in Children?

Brimonidine should not be used in infants younger than 2 years old and should be used with caution in children younger than 6 years [12]. Authors have suggested a weight of at least 18–20 kg before considering brimonidine or apraclonidine. All patients being started on brimonidine and their parents should be warned of the potential for fatigue, lethargy, and unresponsiveness. In the initial clinical trials of brimonidine that evaluated patients aged 2–7 years old, the most common adverse side effect noted was somnolence and decreased alertness (seen in 50–83 % of subjects) as compared to 20–52 % of adults who experienced adverse events [13]. Brimonidine's structure is similar to clonidine's structure, a drug that causes a well-described toxicity in children by stimulating vasomotor centers of the brainstem that suppress the outflow of sympathetic activity (causing reductions in resting heart rate, stroke volume, and total peripheral resistance) and stimulate parasympathetic outflow [4]. Brimonidine is lipophilic and penetrates the blood–brain barrier. It is 7–12-fold more α-2 selective than clonidine. In infants less than 6 months of age, brimonidine's effects on the central nervous system include unresponsiveness, lethargy, rapid breathing, and stupor. These effects can be fatal. This effect has been reported to occur within a few minutes to 30 min of topical application. Fortunately, in case reports of these serious adverse effects, upon discontinuation of brimonidine the affected infants recovered without sequelae [14, 15]. Some clinicians believe that apraclonidine 0.5 % is safer for use in children than brimonidine; however, in infants there have been reports of severe respiratory depression, hypotension, and CNS changes where apraclonidine was used as a diagnostic test for Horner's syndrome [16].

51.6 What Cautions Are There with Prostaglandin Analogues in Children?

There is little peer-reviewed literature on pediatric use of prostaglandin analogues. Results of latanoprost use have been reported in two studies of Sturge-Weber-associated glaucoma and in one study of a mixed population of pediatric glaucomas. In all studies, the recurring theme is that latanoprost seems to work better in older children. In the study of mixed glaucoma, children who responded (defined as ≥15 % drop in IOP) had a mean age of 11.1 years (range, 8.8–13 years) vs. those who did not respond with a mean age of 5.0 years (range, 0.7–14.9 years). Those that carried a diagnosis of juvenile open angle glaucoma were most likely to experience a significant IOP decrease. Side effects of latanoprost are similar to those seen in adults—conjunctival hyperemia, increased iris pigmentation, and lash growth. One case report from the German literature reports heavy sweat secretion in a child with aniridia and glaucoma 2 h after latanoprost administration [17]. There is also a report of sleep disturbance [18, 19]. Several explanations have been provided for the disappointing results of latanoprost use in children compared to adults. The uveoscleral outflow pathway may be abnormal in young children with glaucoma compared to that in adults, similar to the abnormality/immaturity of trabecular meshwork outflow. Furthermore, the surgery that children with congenital glaucoma have undergone may affect their uveoscleral outflow.

51.7 What Cautions Are There with Parasympathomimetics in Children?

Parasympathomimetics have not been found to be very effective in primary congenital glaucoma, presumably due to angle dysgenesis. A paradoxical

rise in IOP has even been seen. The recommended dosage for children 1 month to 2 years of age is 0.5 % or 1 % three times daily and four times daily in children aged 2–18 years. Pilocarpine is poorly tolerated in many children due to induced myopia.

Summary for the Clinician

- Most IOP-lowering medications are not licensed for use in children; however, they have been used effectively and safely in children.
- Younger children have smaller blood volumes and immature enzyme pathways, making them more susceptible to systemic side effects.
- The younger the child, the greater the risk of serious side effects. Toxic effects in children may present with different signs/symptoms than those seen in adults.
- Always describe in detail signs/symptoms of adverse drug effects to caretakers in order to educate them about potentially serious side effects.
- Beta-blockers can cause apnea and bradycardia. Start with a 0.25 % concentration or once daily 0.1 % gel formulation.
- Carbonic anhydrase inhibitors, systemic or topical, have the same side effect profile as in adults. They must be appropriately dosed.
- Adrenoreceptor agonists, such as brimonidine, should not be used in infants less than 2 years and with caution in children who are less than 6 years due to reports of unresponsiveness, lethargy, rapid breathing, and stupor.
- Prostaglandin analogues work better in older children.
- Parasympathomimetics can have a paradoxical effect in congenital glaucoma and tend to be poorly tolerated by children.

51.8 Do Topical Steroids Induce a Different Steroid Response in Children?

In adults, the ocular hypertensive response to steroids is well-documented and frequently seen in the clinical setting. The IOP increase and outflow facility reduction after subjecting a normal adult population to topical corticosteroid treatment (0.1 % dexamethasone) was first reported by Armaly [20]. In 1963, he reported three levels of steroid responders: low responders were subjects with an IOP increase of less than 6 mmHg, intermediate responders were those with an IOP elevation between 6 and 15 mmHg (35 % of his population), and high responders were those with an IOP increase greater than 15 mmHg (5 % of his population). It was also reported that people aged 40 years and older had IOP increases more frequently than those 18–30 years of age.

In children, information regarding the ocular hypertensive response primarily comes from studies using postoperative steroids after strabismus surgery in anatomically normal eyes. In these studies, children with a known family history of glaucoma were excluded. These studies show us that the ocular hypertensive response in children is different from that seen in adults. It can be more severe in relation to peak IOP, time to peak IOP, and dosage of steroid used. The response also appears to be age-dependent, in that children younger than 6 years of age are more sensitive than those older than 6 years [21].

In a study that compared topical dexamethasone 0.1 % four times daily vs. twice daily for 4 weeks in 3–10-year-olds undergoing strabismus surgery, peak IOPs were higher in the four times daily group (14.0–50.3 mmHg) than in the twice daily group (11.0–41.3 mmHg). The net increase was as high as 36.3 mmHg in the four times daily group. One third of patients had an IOP of at least 30 mmHg after steroid treatment and one third were classified as high-responders by the Armaly classification (IOP increase > 15 mmHg). The mean time to reach peak IOP was 15 days (range 1–27 days) with the last IOP measured on postoperative day 55.

Children who were 6 years of age and younger had higher net IOP increase (mean 16.3 ± 10 mmHg) compared to older children (mean 11.9 ± 6.2 mmHg) [22]. Ocular hypertensive response has also been seen with dexamethasone ointment applied to eyelids after epiblepharon surgery in children aged 3–13 years, although the peak IOPs were not as dramatic as those seen with topical dexamethasone drops. In this study, children less than 5 years of age had higher peak IOP [23]. With different dosages of fluorometholone (FML), a steroid that has been reported to have a reduced risk of increasing IOP [24], a dose-dependent response is also seen. In a comparison of FML 0.1 % six times daily in one eye vs. four times daily in the contralateral eye for 4 weeks in children 3–9 years of age, a greater and quicker IOP response was seen in those dosed six times daily. Peak IOPs were as high as 31 mmHg with net increases as high as 16 mmHg [25]. Two other studies, however, reported no significant ocular hypertensive response after topical dexamethasone for strabismus surgery or for vernal keratoconjunctivitis. In one study, the authors offer the view that the majority of their subjects were older than 10 years of age, which may account for the lack of response [26]. In another study, the average age was 9.7 years [27].

Many theories exist regarding the mechanism of steroid-induced IOP elevations, including effects on gene regulation, alterations of ion transport function, and increased extracellular lamina deposits in the trabecular meshwork [28–30]. The functional immaturity of the pediatric trabecular meshwork is often used to explain the corticosteroid response in children. Immaturity may lead to greater resistance to aqueous outflow. Although the trabecular meshwork is fully present at birth, it is not completely mature until approximately 8 years of age [31]. An age-dependent response to steroids has also been seen in rabbits. It correlates with the concentration and distribution of glycosaminoglycans in the anterior segment of the eyes. Young rabbits have demonstrated a steroid response, whereas older rabbits have not [32, 33].

Summary for the Clinician

- The steroid response can be quicker (average time 15 days) and more severe in children.
- The steroid response is more likely to occur in younger children—the exact age cut-off is unknown but 5–6 years of age was identified in a few studies.
- The steroid response in children is dose-dependent and has even been seen with fluoromethalone.
- The steroid response may have something to do with the functional immaturity of the trabecular meshwork, which does not mature until approximately 8 years of age.

References

1. Wallace DK, Steinkuller PG. Ocular medications in children. Clin Pediatr. 1998;37:645–52.
2. Patton TF, Robinson JR. Pediatric dosing considerations in ophthalmology. J Pediatr Ophthalmol. 1976; 13:171–8.
3. Shell JW. Pharmacokinetics of topically applied ophthalmic drugs. Surv Ophthalmol. 1982;26:207–18.
4. Levy Y, Zadok D. Systemic side effects of ophthalmic drops. Clin Pediatr. 2004;43:99–101.
5. Berlin RJ, Lee UT, Samples JR, et al. Ophthalmic drops causing coma in an infant. J Pediatr. 2001;138: 441–3.
6. Passo MS, Palmer EA, Van Buskirk EM. Plasma timolol in glaucoma patients. Ophthalmology. 1984; 91:1361–3.
7. Moore W, Nischal KK. Pharmacologic management of glaucoma in childhood. Paediatr Drugs. 2007;9: 71–9.
8. Chang L, Ong EL, Bunce C, et al. A review of the medical treatment of pediatric glaucomas at Moorfields Eye Hospital. J Glaucoma. 2013;22: 601–7.
9. Ott EZ, Mills MD, Arango S, et al. A randomized trial assessing dorzolamide in patient with glaucoma who are younger than 6 years. Arch Ophthalmol. 2005;123: 1177–86.
10. Morris S, Geh V, Nischal KK, et al. Topical dorzolamide and metabolic acidosis in a neonate. Br J Ophthalmol. 2003;87:1052–3.

11. Futagi Y, Otani K, Abe J. Growth suppression in children receiving acetazolamide with antiepileptic drugs. Pediatr Neurol. 1996;15:323–6.
12. Enyedi LB, Freedman SF. Safety and efficacy of brimonidine in children with glaucoma. J AAPOS. 2001;5:281–4.
13. Daubert GP. Is brimonidine ophthalmic a safe therapy for infants? J Clin Pharm Ther. 2006;31:289–92.
14. Carlsen JO, Zabriskie NA, Kwon YH, et al. Apparent central nervous system depression in infants after the use of topical brimonidine. Am J Ophthalmol. 1999; 128:255–6.
15. Korsch E, Grote A, Seybold M, et al. Systemic adverse effects of topical treatment with brimonidine in an infant with secondary glaucoma. Eur J Pediatr. 1999;158:685.
16. Watts P, Satterfield D, Lim MK. Adverse effects of apraclonidine used in the diagnosis of Horner's syndrome in infants. J AAPOS. 2007;11:282–3.
17. Schmidtborn F. Systemic side-effects of latanoprost in a child with aniridia and glaucoma. Ophthalmologe. 1998;95:633–4.
18. Enyedi LB, Freedman SF, Buckley EG. The effectiveness of latanoprost for the treatment of pediatric glaucoma. J AAPOS. 1999;3:33–9.
19. Enyedi LB, Freedman SF. Latanoprost for the treatment of pediatric glaucoma. Surv Ophthalmol. 2002; 47:S129–32.
20. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. Invest Ophthalmol. 1963;4:187–97.
21. Brookes JL, Khaw PT. Steroid response in children. Clin Experiment Ophthalmol. 2005;33:229–30.
22. Lam DS, Fan DS, Ng JS, et al. Ocular hypertensive and anti-inflammatory responses to different dosages of topical dexamethasone in children: a randomized trial. Clin Experiment Ophthalmol. 2005;33:252–8.
23. Lee YJ, Park CY, Woo KI. Ocular hypertensive response to topical dexamethasone ointment in children. Korean J Ophthalmol. 2006;20:166–70.
24. Akingbehin AO. Comparative study of the intraocular pressure effects of fluorometholone 0.1% versus dexamethasone 0.1%. Br J Ophthalmol. 1983;67: 661–3.
25. Fan DS, Ng JS, Lam DS. A prospective study on ocular hypertensive and antiinflammatory response to different dosages of fluorometholone in children. Ophthalmology. 2001;108:1973–7.
26. Khan HA, Amitava AK. Topical diclofenac versus dexamethasone after strabismus surgery: a double-blind randomized clinical trial of anti-inflammatory effect and ocular hypertensive response. Indian J Ophthalmol. 2007;55:271–5.
27. Biedner BZ, David R, Grudsky A, et al. Intraocular pressure response to corticosteroids in children. Br J Ophthalmol. 1980;64:430–1.
28. Dickerson Jr JE, Steely Jr HT, English-Wright SL, et al. The effect of dexamethasone on integrin and laminin expression in cultured human trabecular meshwork cells. Exp Eye Res. 1998;66:731–8.
29. Putney LK, Brandt JD, O'Donnell ME. Effects of dexamethasone on sodium-potassium-chloride cotransport in trabecular meshwork cells. Invest Ophthalmol Vis Sci. 1997;38:1229–40.
30. Lo WR, Rowlette LL, Caballero M, et al. Tissue differential microarray analysis of dexamethasone induction reveals potential mechanisms of steroid glaucoma. Invest Ophthalmol Vis Sci. 2003;44: 473–85.
31. Reme C, d'Epinay SL. Periods of development of the normal human chamber angle. Doc Ophthalmol. 1981;51:241–68.
32. Knepper PA, Breen M, Weinstein HG, et al. Intraocular pressure and glycosaminoglycan distribution in the rabbit eye: effect of age and dexamethasone. Exp Eye Res. 1978;27:567–75.
33. Knepper PA, Collins JA, Frederick R. Effects of dexamethasone, progesterone, and testosterone on IOP and GAGs in the rabbit eye. Invest Ophthalmol Vis Sci. 1985;26:1093–100.

Pediatric Glaucoma: Angle Surgery and Glaucoma Drainage Devices

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Helen H. Yeung and David S. Walton

Core Messages

- Goniotomy is an important procedure for many children with glaucoma. Preoperative gonioscopy is essential preparation, as is careful attention to surgical instrumentation, surgical technique, and to postoperative care.
- Trabeculotomy is an alterative goniosurgical procedure that does not require a clear view of the angle.
- Whether to perform goniosurgery, trabeculectomy, or glaucoma drainage device surgery is a multifactorial clinical decision not easily represented in simple algorithms. Accurate diagnostic classification, gonioscopy, and consideration of previous failed surgery are essential elements to consider.
- Glaucoma drainage device surgery may be performed for most children of all ages and is relatively safe. Complications occur frequently and may relate to the drainage plate or drainage tube mal-position or exposure. Clinical failure most frequently relates to plate encapsulation.
- Tube-shunt surgery for children is technically similar to the procedure for adults.

52.1 How Do I Perform Goniosurgery?

52.1.1 How Do I Perform a Goniotomy?

Personal preference is appropriate when planning for a goniotomy. Ocular fixation, an operating gonioscopy lens, a magnification source, and an instrument for intraocular incision of the trabecular meshwork (TM) are essential to enable the procedure (Table 52.1). Following the preoperative examination, I view the angle again with the operative instrumentation to reinforce the landmarks to guide the trabecular meshwork incision. Following prep and draping fixation, forceps are placed typically on the vertical recti (Others prefer limbal traction sutures to control eye position). I most often use a headlight, 2.3X loupes, and a Barkan style operating lens. The patient's head is rotated 20° away from the surgeon to allow the escape of any air that may intrude under the lens during surgery. The lens is

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Table 52.1 Goniotomy instruments and supplies

Surgical instruments
Loupe and head-mounted light, or tilting surgical microscope
Locking fixation forceps [3]
Castroviejo forceps (0.3)
Fine needle holder, jewelers forceps, infant lid speculum
Operating gonioscopy lenses: small, medium, large
Goniotomy knife (e.g., Storz SP7-62233, Baush & Lomb Incorp, Rochester, NY), or 25-gauge operating needles
Medications and supplies
Balanced saline solution
Apraclonidine 0.5 %
Viscoelastic (optional for anterior chamber deepening)
10–0 absorbable suture (Vicryl 448-G, Ethicon Inc, Somerville, NJ)
70 % isopropyl alcohol
#15-BD blade
30-gauge corneal irrigation needles

placed on the cornea and held in place with my left hand. I use a tapered needle knife and this is entered into the AC directed towards the pupil (a long passage through the cornea makes rotation of the knife more difficult). I view the knife point crossing the AC and engage the TM. I then sweep the incision to the right in a backhanded motion followed by return of the knife to the point of initial engagement and then sweep to the left (forehanded). The knife is carefully withdrawn to avoid expanding the corneal incision width. The anterior chamber is reformed and the wound held closed with jeweler forceps. If aqueous leakage persists, a 10–0 Vicryl stitch is placed to secure the anterior chamber.

52.1.2 What Can I Do Technically to Perform a Better Goniotomy?

The goniotomy procedure is elegantly simple and requires minimal equipment; however, *preparation* for this procedure is essential for its success. In the operating room, gonioscopic examination of the filtration angle allows reassessment of the patient's candidacy for success with goniotomy and prepares the surgeon for the procedure by redefining the target trabecular meshwork (TM) and by assuring the presence of an adequate view of the angle for surgery. Of note, the view of the angle during surgery rarely equals the pre-surgery examination view qualitatively; something to take into account when planning for surgery.

The two most common causes of poor angle visualization in young children with glaucoma are diffuse epithelial edema and localized stromal edema associated with breaks in Descemet's membrane. During the gonioscopic exam, epithelial edema can be quantified best by focusing on the epithelium and noting the intensity of epithelial microcysts present in light reflected from the iris. Only the corneal opacification secondary to epithelial edema is corrected by removal of epithelium (stromal edema is not improved by this maneuver). When necessary, the epithelium is carefully peeled off to create a clear window on the surgeon's side of the cornea extending to the visual axis. This procedure is performed after selecting the meridian for knife entry that allows an optimal view to either side of any stroma opacity.

Preoperative preparation insures that suitable instrumentation for a goniotomy will be present (Table 52.1). Locking fixation forceps, operating lenses of various sizes, and the goniotomy knife of the surgeon's choice are essential. Forceps are used to grasp the rectus muscles through the conjunctiva in order to control eye position, and locking forceps are particularly helpful to prevent slippage off the rectus muscles. Operating lenses in various sizes are especially useful to have ready. For example, when performing the procedure on eyes with smaller corneas, a smaller lens allows comfortable entry of the knife through clear peripheral cornea without dimpling of the cornea under the lens, which would impair one's view of the angle. The goniotomy knife used must be in perfect condition. If dulled, anterior chamber (AC) entry will be problematic and attempted incision of the TM will scrape and drag the tissue rather than incise it sharply. Use of

a 25-gauge needle attached to a syringe in place of a gonio-knife has the advantages of permitting fluid injection into the AC should it shallow.

The goniotomy surgeon must plan entry into the AC on the meridian diametrically opposite the desired position of the planned goniotomy (Fig. 52.1). Once the knife has entered the AC, the globe may be rotated around the entry site (using the locking forceps grasping the recti muscles) in either direction to lengthen the incision in the TM both clockwise and counterclockwise of the initial TM contact. Incision for as many clock hours as is comfortably possible should be performed. There is no data relating the success of goniotomy with the number of clock-hours treated. One third of successfully treated eyes with infantile primary congenital glaucoma will require a second goniotomy to achieve complete success. When a nasal entry is desired, an entry site must be selected that allows rotation of the knife handle without encountering the patient's nose.

We believe that anterior chamber (AC) blood reflux during the interval of hypotony following knife removal can be lessened by pretreating the adjacent limbus with 0.5 % apraclonidine; a minimal amount should be administered topically to prevent excessive dosage that can cause the pupil to dilate prior to the goniotomy. Apraclondine may be administered again at the end of the case. Blood reflux is usually brief and promptly responds to reforming the AC and raising the eye pressure. It is helpful, however, to have a 1:16,000 mixture of epinephrine (1 cm^3 of 1:1000 epinephrine into a 15 cm^3 bottle of balanced salt solution) prepared ahead of time to treat bleeding that is more persistent. This epinephrine mixture can be injected into the AC with an air bubble, which helps tamponade the bleeding until epinephrine has an opportunity to take effect.

Postoperatively, it is beneficial to instruct parents to keep the child's head elevated at all times for 4 days to lessen the risk of recurrent reflux of blood into the AC. Sleeping in a car seat can be very helpful to accomplish this positioning.

52.1.3 What Can I Do Technically to Perform a Better Trabeculotomy ?

The classic Harms trabeculotomy is an alternative goniosurgical procedure indicated for those glaucomas that have been reported to respond to goniosurgery. Trabeculotomy is performed using a standard operating microscope and does not require a clear view of the filtration angle. Following a limbal peritomy, Schlemm's canal is unroofed with a radial groove under a scleral flap. Schlemm's canal is then canalulated with a prolene suture or with lighted trabeculotomy probes (iTrack catheter, Ellex Incorp); a cleft into the AC from Schlemm's canal is then created. It has been reported that Schlemm's canal cannot be located in 11–15 % of cases, so one must be prepared with an alternative plan if trabeculotomy cannot be performed successfully [1].

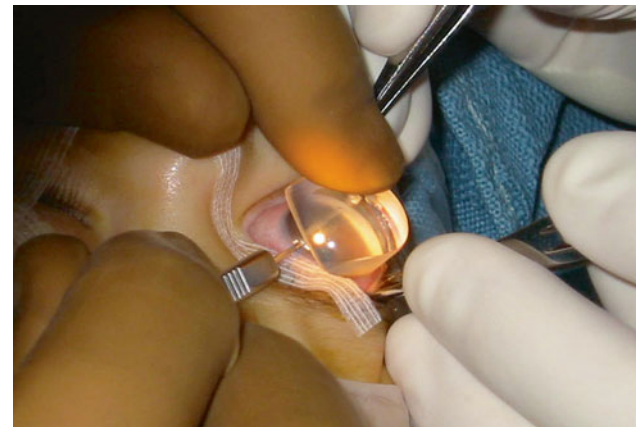

Fig. 52.1 The goniotomy procedure with globe held in position by fixation forceps

It is helpful to place limbal traction sutures at 12 and 6 o'clock to fixate the eye in a moderately adducted or abducted position (9 and 3 o'clock if a combined trabeculectomy is planned) and to stabilize the eye for further surgery. Children often possess pathologic thinning of the peripheral cornea and limbus. These sutures should be placed with care using 6–0 silk with tapered needles to avoid unplanned entry into the AC. Traction sutures in this position also allow desired rotation of the eye to facilitate the planned limbal surgery.

Typically, a triangular scleral flap is advised for this procedure; however, we recommend that the flap be rectangular. Pediatric scleral flaps typically shrink in size. A rectangular flap will help to insure the presence of adequate tissue for closure, which becomes important if there is persistent active flow of aqueous fluid at the conclusion of trabeculotomy or if a trabeculectomy is concurrently performed.

A corneal paracentesis should always be created prior to AC entry. An in-and-out stroke with the narrow Wheeler knife produces an adequate opening that does not require suture closure. Deepening of the AC may be necessary prior to use of the trabeculotomy probes.

Following knife entry into Schlemm's canal, perpendicular to its circumferential direction, it is helpful to snip the roof of Schlemm's canal on the right and left to ease its canalization. Injection of a small amount of viscoelastic into the canal is also helpful before canalization. The Harms type trabeculotomy probe is helpful to facilitate movement into the AC on a single plane anterior to the iris. The probe offered by Katena (Katena Instrument Company, Denville, NJ) is tapered and canulated very nicely.

With rotation of the probe into the AC, the surgeon must first look for the appearance of the distal tip of the instrument forcing the trabeculum centripetally in the mid AC, versus anterior entry into Descemet's membrane or posteriorly into the iris. Once identified, the appropriate plane of movement can be confirmed or modified followed by continued rotation to perforate the angle tissue. Rotation should be continued but not so far as to open the TM in front of the scleral flap and risk rapid collapse of the AC

If a 360° suture trabeculotomy is planned, a 6–0 Prolene suture (Ethicon, Somerville, NJ) must be available. Alternatively, the iTrack catheter may be used which also permits injection of a viscoelastic into schlemn's canal [2].

52.1.4 Is the Trabectome Instrument Which Performs Goniotomy Ab Interno Useful in Children?

Ab interno trabeculotomy with the Trabectome has been performed primarily in adults with glaucoma [3]. The Trabectome tip is inserted through the trabecular meshwork into Schlemm's canal and the TM tissue is ablated in clockwise and/or counterclockwise directions. In order to perform this procedure, a clear view through the cornea is needed to visualize the angle structures. Theoretically, it seems possible that the Trabectome may be useful in cases of primary congenital glaucoma or in cases of glaucoma secondary to uveitis in children. In the literature, however, there has been no case series reported on the use of Trabectome in the childhood glaucomas [4].

52.1.5 What Complications Can Be Expected Following Goniosurgery and How Do I Manage Them?

Complications following goniotomy and trabeculotomy procedures are infrequent. Most commonly, one sees the spontaneous occurrence of a reflux hyphema in the immediate postoperative period after both procedures. This occurs most frequently during periods of sleep presumably due to lower intraocular pressures (IOP). It has been clinically useful to encourage head elevation during sleep to reduce the episcleral venous pressure and risk for additional blood reflux into the AC. Bedtime topical 0.5 % apraclonidine also may be helpful, but care must be used in using

alpha agonists in young children. In the early postoperative period, IOP is monitored frequently. If IOP elevates to a level greater than preoperative pressures, as may occur secondary to a large hyphema or to retention of intraoperative viscoelastic, an immediate AC washout may be indicated to prevent iris, lens, and optic nerve injury. This is typically accomplished through a small paracentesis employing an injection of air to promote the exit of blood or the viscoelastic and is followed by reformation of the AC.

Summary for the Clinician

- Preoperative planning is important for successful goniotomy. Have available a sharp gonioknife or 25-gauge needle and alternately sized goniolenses. Perform preoperative gonioscopic examination of the angle to orient yourself to the patient's anatomy.
- Edematous epithelium can be peeled off if it obscures one's view of the angle.
- Topical apraclonidine 0.5 % and intracameral 1:16,000 epinephrine can be used to minimize or control AC bleeding.
- For trabeculotomy, create a rectangular flap and then dissect perpendicularly to the scleral fibers until Schlemm's canal is reached. Harm's trabeculotomy probes or a suture (or catheter) are very useful to create the desired fistula.
- Postoperatively, have the child's head continuously elevated for 4 days—sleeping in a car seat can help to accomplish this positioning.
- Complications are infrequent following goniosurgery. Hyphema is most common. Acute elevation of IOP postoperatively is an indication for immediate corrective surgery.

52.2 How Do I Perform Glaucoma Drainage Devices (GDD) in Children?

52.2.1 What Can I Do Technically to Perform a Better GDD Implantation?

The glaucoma implant procedure begins by creating adequate exposure in the operative field. For infants and small children, a pediatric solid blade lid speculum is very helpful. Performing a single snip lateral canthotomy can improve exposure. The placement of limbal traction sutures at 9 and 3 o'clock further expose the field for surgery. For superotemporal positioning of the plate, the nasal traction sutures should be placed somewhat more superiorly to cause inward rotation of the globe to occur with downward traction, which brings the superior temporal quadrant into better position for surgery. A peritomy is performed for approximately 2 h, followed by short radial cuts of approximately 2 mm. In children, Tenon's capsule is quite well-defined. It terminates at Chen's line located about 1.5 mm posterior to the limbus where it fuses with the sclera at that position. To enter the subtenon's space, this adherence to the sclera is cut widely. The locations of the adjacent rectus muscles are next identified; this can be done best gently with a slender tenotomy muscle hook.

The GDD plate is usually trimmed for placement on a child's eye. This facilitates positioning of the plate more superiorly adjacent to the superior rectus muscle, which permits the tube to enter the AC more superiorly. Shortening the plate may be indicated to prevent proximity to the optic nerve, especially with nasal placement of the plate in a nonbuphthalmic eye. In order to thin the profile of the Ahmed valve for small eyes, the pocket that the valve and tube sit in can be split apart with a Jewelers forceps and then replaced in the pocket with only the front polypropylene plate over the valve mechanism.

Following its irrigation and establishment of flow, the implant's plate is positioned in the subtenon's space approximately 6–7 mm behind the

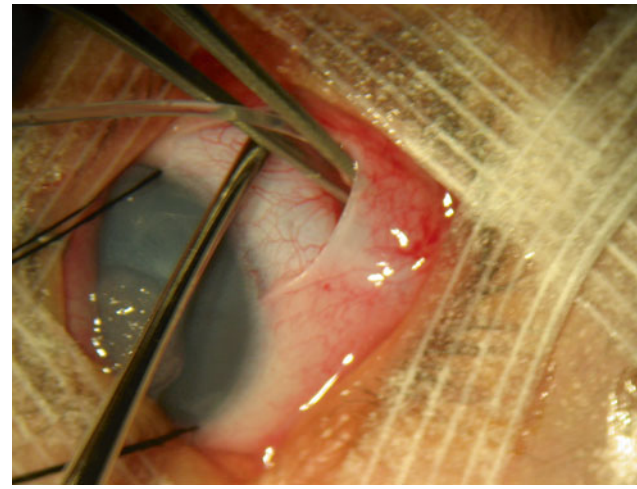

Fig. 52.2 GDD insertion procedure. Sweep with a muscle hook releases Tenon's capsule from drainage device plate

limbus. After initial positioning, the implant may tend to float anteriorly in spite of the ability to move it posteriorly with little resistance. This tendency to float anteriorly can be attributed to adherence of Tenon's capsule to the plate. It is corrected by a maneuver that should be repeated with every plate insertion. Introduce a Graefe muscle hook under the implant (against sclera) and then bring it around the implant lifting the Tenon's capsule away from the anterior surface of the implant plate (surface facing Tenon's capsule) before the hook's removal from the field (Fig. 52.2). Repeat the procedure on the opposite side and the implant will fall posteriorly now free of the Tenon's attachments.

After suturing the implant to sclera, the tube is trimmed to the desired length with a beveled cut. A paracentesis is created; we prefer a Wheeler knife for this entry through the peripheral clear cornea. This same knife is then used at the tube entry site to enter the AC at an appropriate position and plane. This small opening allows the follow-up 23-gauge needle to enter more easily into the AC. Tube entry directed towards the iris is indicated to discourage postoperative anterior rotation of the tube into contact with the cornea. The scleral portion of the tube can then be secured to the sclera using 8–0 Vicryl (Ethicon Inc) stitches. Use of nonabsorbable sutures to secure the tube to the sclera minimizes later erosion through the conjunctiva. The entry site should allow for a narrow bridge of limbal tissue to remain as an anchor for patch graft material (processed pericardium, sclera, or cornea) over the tube. The conjunctiva is pulled anteriorly and positioned tightly along the limbus with the tension created by buried 9–0 Vicryl stitches at each corner.

To prevent prolonged postoperative hypotony, we occlude the tube with a 7–0 Vicyrl suture. The position of the initial paracentesis site should be accurately recorded for use postoperatively if reformation of the AC becomes indicated.

52.2.2 What Are the Potential Complications of Childhood GDD Surgery?

GDD (both valved and nonvalved devices) can be successfully implanted for childhood glaucoma [5, 6]; however, complications are common [5, 6]. Failure to control the IOP after GDD implantation is typically secondary to tight fibrous encapsulation around the plate connected to the tube. The most frequently occurring postsurgical complications relate to the actual tube [6]. It may become blocked in the AC by iris or with vitreous in aphakic eyes. Anterior rotation of the tube inside the AC may result in tube-corneal touch with resultant blockage of the tube, injury to the cornea (including potential graft failure), and externalization of

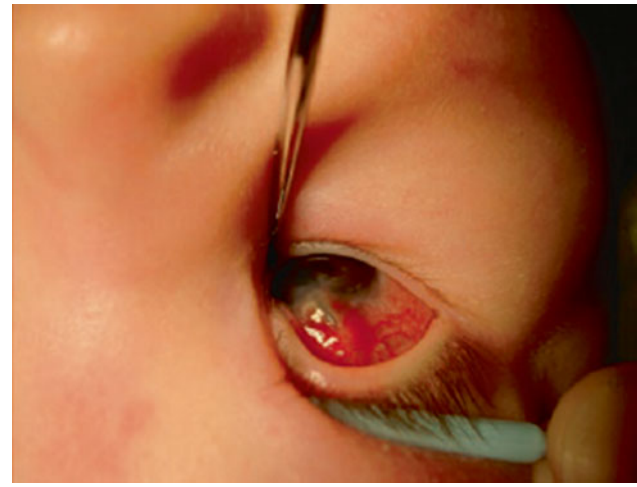

Fig. 52.3 Glaucoma drainage tube exposure through the conjunctiva in a child

the tube through the cornea. A frequent tube-related complication is corectopia caused by peripheral contact between the iris and tube with secondary drawing of the iris and pupil towards the tube insertion site. The tube or plate may also extrude through the anterior bulbar conjunctiva (Fig. 52.3), which places the globe at significant risk for bacterial endophthalmitis [7]. Preseptal cellulitis has also been reported in a small percent of children who have undergone GDD implantation [4].

Persistent hypotony may result in choroidal effusion and chronic retinal detachment. I do not think the valved implants prevent postoperative hypotony compared to nonvalved implants, and I often deactivate the valves on the Ahmed plate in order to achieve a thinner device for insertion in small orbits. Low-grade chronic anterior intraocular inflammation (iridocyclitis) may also follow pediatric GDD insertion. With this complication, older children will complain of pain and show evidence of photophobia. In infants, symptoms of this complication are more subtle: persistent photophobia, iris hypervasculaity, AC fibrin on the tube, poor pupillary dilation, and unexpected posterior pigment release with pigment accumulation in the angle are seen. Tube-shunt removal is usually necessary to treat this condition. A deformity consisting of outward bulging of the inferior eyelid occurs frequently with functioning implants that are placed infero-temporally. Horizontal and vertical strabismus, as well as limitation of eye movement, occur frequently with GDDs [8] and may be more frequently associated with large implants that become incorporated with and that are located under the extraocular muscles. I prefer the Ahmed implant because of its anterior–posterior orientation versus the circumferential orientation of the Baerveldt devices.

Summary for the Clinician

- Adequate exposure is important for easy GDD implantation—this can be increased with a pediatric speculum, snip lateral canthotomy, and well-placed traction sutures.
- Tenon's capsule can cause the GDD plate to float forward before it is secured to sclera. A sweep of the Tenon's capsule with a muscle hook can prevent this from occurring. The tube insertion should be directed towards the proximal iris leaf to discourage postoperative tube-corneal touch.
- A paracentesis should be made and its position noted for possible postoperative use in shallow chambers and hypotony.
- The GDD plate can be trimmed to a more appropriate size for the pediatric eye.

52.3 Is a GDD Preferred Over Trabeculectomy in Children? Is Age Important in the Selection of This Surgery? What Other Factors Should Be Considered?

If all other factors were identical, I would favor trabeculectomy over GDD surgery. A GDD can successfully follow a trabeculectomy at one site, but the reverse scenario is not necessarily true.

A GDD can be performed for a child of any age. The full adult size silicone implants are preferable. The pliable plate can be trimmed to reduce its size as necessary for smaller eyes. Successful trabeculectomy surgery in the first 6 months of life is difficult to achieve [9]; however, Mandal has reported successful combined trabeculectomy-trabeculotomy surgery for infants [10]. Tube-shunt surgery appears to be more reliable for younger glaucoma patients, especially for those under 6 months of age [11]. Given the uncertain results with trabeculectomy in all infants and the poor response to goniosurgery in infants with Newborn Primary Congenital Glaucoma, glaucoma drainage device surgery exists as an important alternative for these very young children [12].

Other factors that determine the final choice of surgery include a history of previous ocular surgery and the results of previous glaucoma surgery, the condition of the conjunctiva at the site of potential surgery, parental attention to eye care and patient availability for return visits, general eye health and vision potential, clarity of the cornea, condition of the optic nerve, the condition of the fellow eye, and its vision. For example, trabeculectomy would be favored over a GDD in an older phakic child with an unoperated superior limbal site and who can be followed indefinitely. It would also be preferred in a pediatric eye that possesses good vision that is being threatened by high IOP and whose target IOP is lower than might be expected from a GDD, even if the eye has previously undergone trabeculectomy.

Summary for the Clinician

- Glaucoma drainage devices are a good option for younger children with glaucoma, especially those less than 6 months of age.
- In older children who need a very low pressure, trabeculectomy may be preferable if they are cooperative and reliable and other conditions of the eye make complications such as endophthalmitis less likely.

References

1. Elder MJ. Congenital glaucoma in the West Bank and Gaza Strip. Br J Ophthalmol. 1993;77:413–6.
2. Girkin CA, Marchase N, Cogen MS. Circumferential trabeculotomy with an illuminated microcatheter in congenital glaucomas. J Glaucoma. 2012;21:160–3.
3. Minckler D, Baerveldt G, Ramirez MA, Mosaed S, Wilson R, Shaarawy T, Zack B, Dustin L, Francis B. Clinical results with the Trabectome, a novel surgical device for treatment of open-angle glaucoma. Trans Am Ophthalmol Soc. 2006;104:40–50.
4. Chen TC, Chen PP, Francis BA, Junk AK, Smith SD, Singh K, Lin SC. Pediatric glaucoma surgery: a report by the American academy of ophthalmology. Ophthalmology. 2014;121:2107–15.
5. Chen TC, Bhatia LS, Walton DS. Ahmed valve surgery for refractory pediatric glaucoma: a report of 52 eyes. J Pediatr Ophthalmol Strabismus. 2005;42:274–83.
6. Schotthoerfer EO, Yanovich TL, Freedman SF. Aqueous drainage device surgery in refractory pediatric glaucomas: I. Long-term outcomes. J AAPOS. 2008;12:33–9.
7. Krebs DB, Liebmann JM, Ritch R, Speaker M. Late infectious endophthalmitis from exposed glaucoma setons. Arch Ophthalmol. 1992;110:174–5.
8. Schotthoerfer EO, Yanovich TL, Freedman SF. Aqueous drainage device surgery in refractory pediatric glaucomas: II. Ocular mobility consequences. J AAPOS. 2008;12:40–3.
9. Freedman SF, McCormick K, Cox TA. Mitomycin C-augmented trabeculectomy with postoperative wound modulation in pediatric glaucoma. J AAPOS. 1999;3:117–23.
10. Mandal AK, Bhatia PG, Bhaskar A, Nuthetti R. Long-term surgical and visual outcomes in Indian children with developmental glaucoma operated on within 6 months of birth. Ophthalmology. 2003;111:283–90.
11. Neck AD, Freedman S, Krammer J, et al. Aqueous shunt devices compared with trabeculectomy with mitomycin-C for children in the first two years of life. Am J Opthalmol. 2003;136:994.
12. Walton DS, Katsavounidou G. Newborn primary congenital glaucoma: 2005 update. J Pediatr Ophthalmol. 2005;42:1–9.

Pediatric Glaucoma: Trabeculectomy and Glaucoma Drainage Devices

53

Annette Giangiacomo and Allen Beck

Core Messages

- Goniotomy or trabeculotomy surgery remains the preferred initial treatment for primary congenital glaucoma [12] and may be of benefit in other childhood glaucomas such as open-angle glaucoma associated with uveitis [22].
- Glaucoma drainage devices (GDD) are preferred over trabeculectomy for childhood glaucoma in very young children (pre-school age) and for glaucoma associated with aphakia, due to better efficacy of GDD surgery [5–9, 11–14, 27, 28, 30].
- When trabeculectomy surgery is successful in young children, late-onset bleb-related endophthalmitis is a significant ongoing concern and likely occurs more frequently than in adult patients [6, 15, 18, 40].
- Attention to revision of filtering bleb leaks and mal-positioned tubes can lead to good visual outcomes and successful control of childhood glaucoma [5, 6].

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53.1 Is Trabeculectomy the Preferred Surgery in Children Following Angle Surgery (Goniotomy and Trabeculotomy)?

Usually the answer is no; however there may be some regional variations to practice patterns [8, 17, 24]. Many goniotomy/trabeculotomy failures occur in the first several months after the procedure [12]. Both severity of presentation and age at presentation have been correlated with treatment success in primary congenital glaucoma, with birth-onset, late-onset, and more severe presentations (large corneal diameter and high intraocular pressure (IOP)) correlating negatively with successful glaucoma control [1, 12]. Both goniotomy and trabeculotomy surgery can be repeated (goniotomy up to three procedures) [12]. If repeat angle surgery along with resumption of medical therapy is not successful during infancy, trabeculectomy with adjunctive mitomycin offers a low chance of success [5, 6, 10, 15]. The one exception is the older, phakic school age child for whom mitomycin trabeculectomy has a good chance of success, albeit with a lifelong risk of bleb-related endophthalmitis [6, 10, 15, 17, 25, 36]. In contradistinction to trabeculectomy, GDD surgery offers a reasonable chance of success for glaucoma that has failed angle surgery treatment during the infantile and

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pre-school periods [2, 5, 7, 24]. The risk of endophthalmitis is low with GDD procedures and generally occurs only if the tube or implant becomes exposed [16]. Revision of GDD procedures is more common in very young children due to the higher occurrence of tube-cornea touch and retraction of the tube out of the anterior chamber. However, successful control of the glaucoma can be maintained despite revision of tube-shunt devices [5].

Summary for the Clinician

- Tube-shunt surgery offers a better chance of successful glaucoma control when there is early failure of goniotomy/trabeculotomy.
- Trabeculectomy with mitomycin can be an effective treatment for older (school-age) children, but careful monitoring for signs of bleb leak and infection needs to be performed.

53.2 Is Trabeculectomy Preferred Over Glaucoma Drainage Device Surgery in Children?

Glaucoma drainage device surgery is preferred over trabeculectomy by many pediatric glaucoma specialists. They offer better efficacy for many indications, with a very low risk of bleb-related endophthalmitis [5, 7, 11, 13, 14, 27, 28, 30]. However, technique modifications to trabeculectomy offer the potential for lower risk of late bleb leak and infection [42]. Nonpenetrating procedures are another surgical option in children, with a lower potential for complications than trabeculectomy. Nonpenetrating surgery has a steep learning curve, with initial reports documenting a high conversion rate to trabeculectomy, along with limited intermediate- and long-term efficacy data in congenital glaucoma [26, 37]. At this time, GDD surgery is frequently the best surgical option for many pediatric glaucoma indications after angle surgery.

Summary for the Clinician

- A glaucoma drainage device is preferred over trabeculectomy in aphakic children and for pediatric glaucoma occurring during infancy and early childhood.

53.3 Is There an Age Cut-Off for Performing Trabeculectomy in the Pediatric Age Group?

Trabeculectomy surgery can be performed at any age. However, several studies have documented a reduced success rate in very young children, especially in those under the age of 2 years [5, 6, 15, 36]. The effect of mitomycin C on the tenon's capsule of infants does not appear to provide the inhibition of fibroblast proliferation noted in older children and adults, leading to early bleb failure. Another difficulty with performing trabeculectomy in very young children is monitoring for bleb leaks (Fig. 53.1). Obtaining IOP readings and slit lamp evaluation is frequently difficult in the 1–4 year age range, leading to intermittent exam under anesthesia as the only option for monitoring these children. This age group also frequently develops upper respiratory infection, with the potential for bacterial conjunctivitis such as H. influenza [31]. The combination of these factors leads to an increased potential for bleb-related endophthalmitis, a potentially devastating complication. Older school-age children can usually be monitored in the office setting effectively and can communicate the symptoms of bleb-related infection more easily (Fig. 53.2).

Summary for the Clinician

- Trabeculectomy has been demonstrated to be less effective than tube-shunt surgery below 2 years of age.

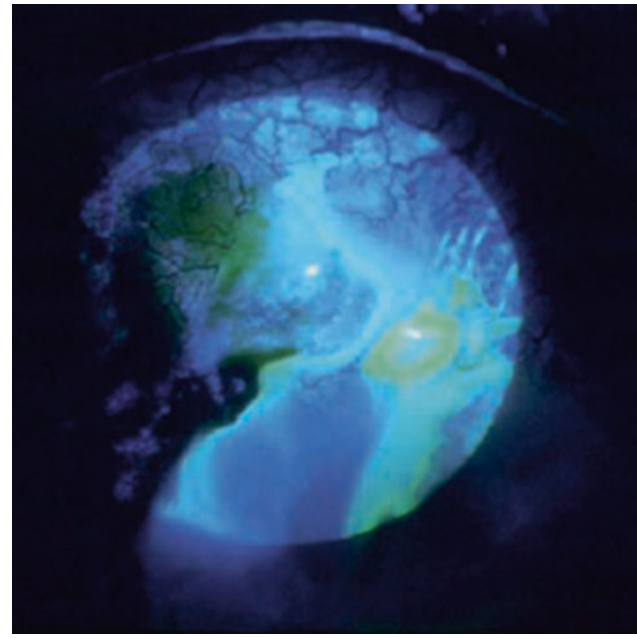

Fig. 53.1 A filtering-bleb leak demonstrated by Seidel testing

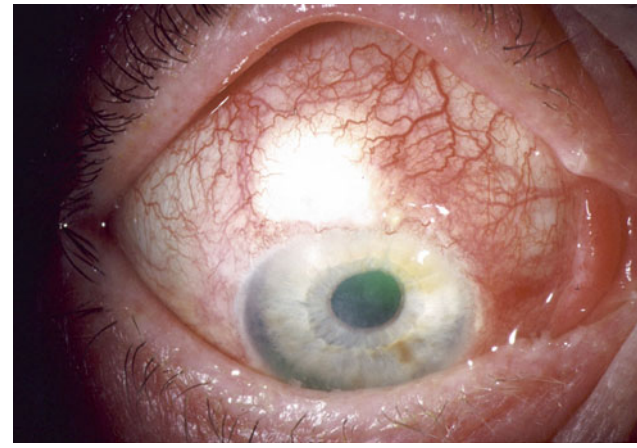

Fig. 53.2 A blebitis or filtering bleb infection demonstrating characteristic "*white on red*" appearance

- The effect of Mitomycin-C on the tenon's capsule of infants appears less than that seen in older children and adults.
- Pre-school children are difficult to evaluate for bleb leaks postoperatively and have a high incidence of bacterial conjunctivitis, making trabeculectomy a less attractive surgery for this age group.

53.4 What Factors Help One Decide for or Against One Surgery Over the Other?

Age of the patient, prior surgical intervention, and the social support of the child are all factors that can help with the surgical decision-making process. Young patient age has already been discussed as a risk factor for trabeculectomy failure,

leading to a greater likelihood that a GDD will be recommended during infancy and in pre-school age groups. Prior surgical intervention, especially congenital cataract surgery, has been shown to be a risk factor for trabeculectomy surgery failure [6, 9], although trabeculectomy with mitomycin can be successful in aphakic patients [41]. Contact lens use has been associated with an increased risk of bleb-related endophthalmitis [20] and also tilts the risk-benefit ratio in favor of GDD surgery. Finally, the social support network for the child is critically important for adequate follow-up and may tilt the axis in favor of a GDD procedure.

Summary for the Clinician

Young patient age, prior surgery, contact lens use, and social support for the child are all important factors in determining the appropriate glaucoma surgical intervention.

53.5 What Complications and Issues Should Be Anticipated in the Intraoperative and Postoperative Periods?

Complications can be divided into intraoperative, initial postoperative, and late postoperative groups.

53.5.1 In Trabeculectomy

Intraoperative Special attention should be paid to flap construction in elastic, buphthalmic eyes to avoid overly thin flaps that can contribute to early hypotony. An excessively large sclerostomy should also be avoided for the same reason. To prevent early hypotony, viscoelastic can be injected into the anterior chamber to maintain higher IOP initially and cycloplegics can be used to rotate the ciliary body backwards minimizing risk of flat chambers. Careful wound closure is important to avoid unnecessary wound leaks.

Initial Postoperative One should look for hypotony complications such as shallow anterior chamber, serous and hemorrhagic choroidal detachments, and wound leak. Shallow anterior chambers usually reform spontaneously, due to the rapid healing response of the child. Chronic hypotony is a concern and a frequent indication for revision if vision reduction is noted.

Late Postoperative Routine monitoring for bleb leaks should be performed. Care-givers must be educated as to the signs and symptoms of bleb-related infection, cataract, and bleb failure.

53.5.2 In Glaucoma Drainage Devices

Intraoperative Tube placement is critical especially during infancy. As the eye grows, the tube can shift position. Placement of tube should be as close to the iris as possible, and posterior chamber or pars plana location in aphakia/pseudophakia even should be considered. An adequate vitrectomy is necessary to prevent tube-block in aphakia/pseudophakia. Expect the length of tube in the anterior chamber to increase during infancy as the globe decreases in size with reduced IOP. Ensure adequate patch graft coverage of the scleral portion of tube and perform careful wound closure to prevent wound dehiscence, which can lead to tube or plate exposure. Use a cohesive viscoelastic to support the anterior chamber with valved tube-shunts to minimize early hypotony complications.

Initial Postoperative Watch for hypotony complications such as shallow anterior chamber, serous, or hemorrhagic choroidal detachments [2, 3]. Early hypotony complications will usually resolve with cycloplegia/observation, while chronic hypotony complications are usually an indication of revision/temporary tube ligation. Development of a hypertensive phase is common and should be managed with IOP-lowering therapy [3]. Early exposure of the patch overlying the

tube should be monitored and may resolve by re-epithelialization, especially if there is only a small amount of exposure along the limbus. Glaucoma drainage device implantation has been shown to induce motility disturbance and strabismus in many children, but none of the children in Schotthoefer's study reported diplopia [35].

Late Postoperative Complications to anticipate are as follows: tube malposition/migration/or retraction (indication for tube repositioning), tube or implant exposure (indication for wound revision and possible patch graft replacement), cataract, chronic inflammation (may require long-term corticosteroid treatment), corneal scarring or edema, endophthalmitis, retinal detachment, iris peaking to region of tube (can be concerning to care-givers, but this is usually simply observed although occasionally optical issue arises due to eccentric pupil location) [32, 34], and failure of tube-shunt device [2, 3, 10, 24, 34]. Failure of Ahmed devices may be caused by fibrovascular ingrowth, particularly into the valve chamber [39]. This type of failure can be treated via removal of fibrovascular ingrowth from the valve mechanism (with subsequent verification of valve function by irrigation of the tube), replacement of the GDD, or placement of a second GDD. Pupillary membranes which do not resolve are a potential amblyopia concern when they occur during infancy and early childhood and may require surgical removal if they do not resolve with medical therapy.

Summary for the Clinician

- Cycloplegia and observation are appropriate for early hypotony complications from trabeculectomy and GDD surgery.
- Return to the operating room for wound dehiscence, persistent pupillary membranes, prolonged hypotony, or tube-cornea touch.

53.6 What Can Be Done Technically to Perform a Better Trabeculectomy in Kids?

Avoid excessively long duration or high concentration of mitomycin-C application (this usually leads to thin, avascular, leak-prone blebs) and use a relatively large area of mitomycin-C application. The authors have used fornix- and limbus-based trabeculectomy with success in kids. Fornix-based approaches have historically been associated with lower more diffuse blebs and are a good approach with some technique modifications as noted by Wells et al. [42]. One author (AB) favors a limbus-based approach with a short application (2–4 min) of 0.25 mg/ml mitomycin-C, broad area of mitomycin-C exposure (placement of sponge or light shield soaked in MMC on the scleral flap, as well as posterior to the flap), and tight wound closure to prevent early leaks. The ideal filtering bleb is no longer high and cystic, but broad, low, and diffuse. Removal of tenon's capsule should be avoided if possible to avoid thin, avascular blebs. Laser suture lysis and releasable sutures can be utilized in school age children who allow gonioscopy to be performed (examination under anesthesia can be used with younger children to perform suture lysis or release, but it is cumbersome and difficult to arrange on a timely basis). 5-Fluorouracil can be used intraoperatively, but post-op injections are more difficult in children and are not widely utilized for this reason [43]. One retrospective study with limited power noted no significant difference with trabeculectomy using mitomycin-C compared to no antifibrotic agent [33]; but other papers note a low rate of success without antifibrotic application due to the rapid healing response of the child [4, 19, 23].

Shallow anterior chambers will usually reform with conservative measures, due to the rapid healing response of children. Topical and depot corticosteroids are a key to successful bleb formation (the author personally favors frequent topical administration with a slow taper over

2–3 months). If there is a successful bleb and IOP control, discuss signs and symptoms of bleb infection with parents/care-givers. Educate the patient and caregivers to avoid eye rubbing. Monitor the bleb periodically for leaks and revise leaky blebs sooner rather than later.

Summary for the Clinician

- Avoid long duration and high concentrations of mitomycin-C with trabeculectomy (author's preference is 2–4 min of 0.25 mg/ml mitomycin-C).
- Avoid tenon's capsule resection, which can lead to thin, avascular blebs.
- Consider a fornix-based surgical approach and/or broad area of mitomycin-C application.
- Surgically revise thin, leaky filtering blebs.

53.7 What Can Be Done Technically to Perform a Better Glaucoma Drainage Device Surgery in Kids?

During infancy and early childhood, the elastic nature of the eye makes tube positioning problematic. Tube-cornea touch is more likely to occur [5]. Corneal decompensation is a long-term risk, which bears continuing evaluation due to the potential life span of the patients being treated with these devices [38]. This complication can be minimized by positioning the tube at a slightly more acute angle toward the iris and by placing the tube as posterior as possible within the anterior chamber [5, 13]. Anticipating some increase in tube length in the eye during early childhood is also helpful, as a young, buphthalmic eye will decrease in size with IOP reduction. Unfortunately, the tube can also retract out of the eye due to movement of the plate posteriorly as it encapsulates, or during a hypertensive phase. The author favors approximately 3 mm of tube in the anterior chamber placement, directing a superior temporal tube towards the superior iris, not toward the pupil. Other alternative placements include the posterior chamber for pseudophakic patients and the pars plana for aphakic patients. Careful attention to adequate vitrectomy is necessary in aphakic patients, especially for pars plana placement (may require the assistance of a vitreo-retinal colleague) (Fig. 53.3). Careful attention to wound closure and use of an adequately sized patch graft (sclera, pericardium, cornea, fascia lata are most commonly used) are important to prevent wound dehiscence and tube exposure. There is no clear evidence of superiority of a particular patch type, but the authors' preference is for use of sclera in most cases [29]. Unlike in trabeculectomy with mitomycin, endophthalmitis is an uncommon event with tube-shunts unless there is exposure. Exposure of the tube or implant is the main risk factor for

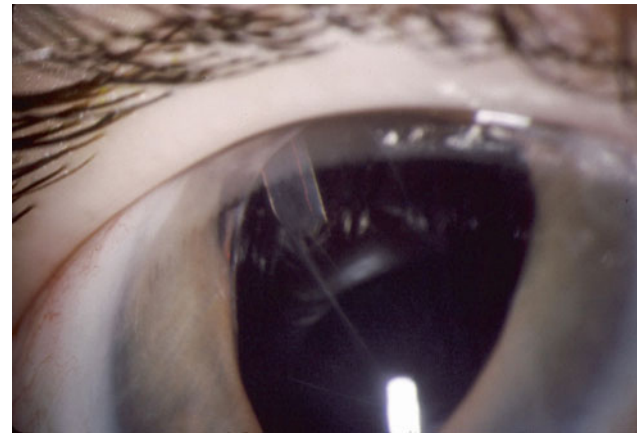

Fig. 53.3 A tube-shunt in an aphakic patient with vitreous incarceration in the tube

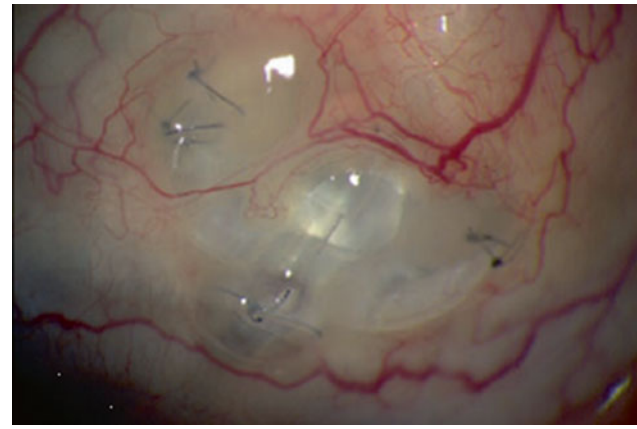

Fig. 53.4 An exposed tube extender device

endophthalmitis and necessitates revision of the tube-shunt device, frequently with an additional patch graft (Fig. 53.4) [16].

Most studies on childhood glaucoma have evaluated Molteno, Ahmed, and Baerveldt implants, with the longest follow-up data available on Molteno implants [5–9, 11, 13, 14, 21, 27, 28, 30]. For glaucomas occurring during infancy, the Ahmed valve offers the advantage of immediate IOP lowering, a potential advantage with an edematous cornea from an amblyopia perspective. Based on information from a comparison of single-plate to double-plate Molteno implants demonstrating superiority of the double-plate model [21], the author favors use of either the adult-size Ahmed implant or a 350 mm^2 Baerveldt implant ligated with a 6–0 polyglactin suture, dependent on the age of the child and the need for more rapid IOP control. For microphthalmic eyes, the pediatric Ahmed implant or the single-plate Molteno is technically easier to place and likely provides sufficient surface area for these smaller eyes.

Summary for the Clinician

- Tube-cornea touch is more likely to occur during infancy due to the elastic nature of the eye.
- Surgically revise tube-shunts for tube-cornea touch and for tube or implant exposure.
- Use of adult-sized implants is recommended for adequate surface area to control the glaucoma.

References

1. Al-Hazmi A, Awad A, Zwaan A, et al. Correlation between surgical success and severity of congenital glaucoma. Br J Ophthalmol. 2005;89:449–53.
2. Al-Mobarak F, Khan AO. Two-year survival of Ahmed valve implantation in the first 2 years of life with and without intraoperative mitomycin-C. Ophthalmology. 2009;116:1862–5.
3. Balekudaru S, Vadalkar J, George R, Vijaya L. The use of Ahmed glaucoma valve in the management of pediatric glaucoma. JAAPOS. 2014;18:351–5.
4. Beauchamp GR, Parks MM. Filtering surgery in children: barriers to success. Ophthalmology. 1979;86:170–80.
5. Beck AD, Freedman SF, Kammer J, et al. Aqueous shunt devices compared with trabeculectomy with mitomycin-C for children in the first two years of life. Am J Ophthalmol. 2003;136:994–1000.
6. Beck AD, Wilson WR, Lynch MG, et al. Trabeculectomy with adjunctive mitomycin-C in pediatric glaucoma. Am J Ophthalmol. 1998;126:648–57.
7. Budenz DL, Gedde SJ, Brandt JD, et al. Baerveldt glaucoma implant in the management of refractory childhood glaucomas. Ophthalmology. 2004;111:2204–10.
8. Bussieres JF, Therrien R, Hamel P, Barret P, Prot-Labarthe S. Retrospective cohort study of 163 pediatric glaucoma patients. Can J Ophthalmol. 2009;44:323–7.
9. Chen TC, Walton DS, Bhatia LS. Aphakic glaucoma after congenital cataract surgery. Arch Ophthalmol. 2004;122:1819–25.

10. Chen TC, Chen PP, Francis BA, Junk AK, Smith SD, Singh K, Lin SC. Pediatric glaucoma surgery. Ophthalmology. 2014;11:2107–15.
11. Coleman AL, Smyth RJ, Wilson MR, et al. Initial clinical experience with the Ahmed glaucoma valve implant in pediatric patients. Arch Ophthalmol. 1997;115:186–91.
12. DeLuise VP, Anderson DR. Primary infantile glaucoma (congenital glaucoma). Surv Ophthalmol. 1983;28:1–19.
13. Djodeyre MR, Calvo JP, Gomez JA. Clinical evaluation and risk factors of time to failure of Ahmed glaucoma valve implant in pediatric patients. Ophthalmology. 2001;108:614–20.
14. Fellenbaum PS, Sidoti PA, Heuer DK, et al. Experience with the Baerveldt implant in young patients with complicated glaucomas. J Glaucoma. 1995;4:91–7.
15. Freedman SF, McCormick K, Cox TA. Mitomycin-C augmented trabeculectomy with post-operative wound modulation in pediatric glaucoma. J AAPOS. 1993;3:117–24.
16. Gedde SJ, Scott IU, Tabandeh HT, et al. Late endophthalmitis associated with glaucoma drainage implants. Ophthalmology. 2001;108:1323–7.
17. Giampani Jr J, Borges-Giampani AS, Carami JCE, Oltrogge EV, Sussana Jr R. Efficacy and safety of trabeculectomy with mitomycin c for childhood glaucoma: a study of results with long-term follow-up. Clinics. 2008;64:421–6.
18. Greenfield DS, Suner IJ, Miller MP, et al. Endophthalmitis after filtering surgery with mitomycin. Arch Ophthalmol. 1996;114:943–9.
19. Gressel MG, Heuer DK, Parrish II RK. Trabeculectomy in young patients. Ophthalmology. 1984;91:1242–6.
20. Gupta N, Weinreb RN. Filtering bleb infection as a complication of orthokeratology. Arch Ophthalmol. 1997;115:1076.
21. Heuer DK, Lloyd MA, Abrams DA, et al. Which is better? One or two? A randomized clinical trial of single-plate versus double-plate Molteno implantation for glaucomas in aphakia and pseudo-phakia. Ophthalmology. 1992;99:1512–9.
22. Ho CL, Wong EY, Walton DS. Goniosurgery for glaucoma complicating childhood uveitis. Arch Ophthalmol. 2004;122:838–44.
23. Inaba Z. Long-term results of trabeculectomy in the Japanese: analysis by life-table method. Jpn J Ophthalmol. 1982;26:361–73.
24. Khan AO, Al-Mobarak F. Comparison of polypropylene and silicone Ahmed valve survival 2 years following implantation in the first 2 years of life. Br J Ophthalmol. 2009;93:791–4.
25. Low S, Hamada S, Kischal KK. Antimetabolite and releasable suture augmented filtration surgery in refractory pediatric glaucomas. J AAPOS. 2008;12:166–72.
26. Luke C, Dietlin TS, Jacobi PC, et al. Risk profile of deep sclerectomy for treatment of refractory congenital glaucoma. Ophthalmology. 2002;109:1066–71.
27. Mills RP, Reynolds A, Emond MJ, et al. Long-term survival of Molteno glaucoma drainage devices. Ophthalmology. 1996;103:299–305.
28. Morad Y, Donaldson CE, Kim YM, et al. The Ahmed drainage implant in the treatment of pediatric glaucoma. Am J Ophthalmol. 2003;135:821–9.
29. Muir KW, Lim A, Stinnett S, Kuo A, Tseng H, Walsh MM. Risk factors for exposure of glaucoma drainage devices: a retrospective observational study. BMJ Open.2014;4(5):e004560.doi:10.1136/bmjopen-2013-004560.
30. Netland PA, Walton DS. Glaucoma drainage implants in pediatric patients. Ophthalmic Surg Lasers. 1993;24:723–9.
31. Patel PB, Diaz MC, Bennett JE, et al. Clinical features of bacterial conjunctivitis in children. Acad Emerg Med. 2007;14:1–5.
32. Pirouzian A, Demer JL. Clinical findings following Ahmed glaucoma valve implantation in pediatric glaucoma. Clin Ophthalmol. 2008;2:123–7.
33. Rodrigues AM, Junior AP, Montezano FT, de Arruda Melo PA, Prata Jr J. Comparison between results of trabeculectomy in primary congenital glaucoma with and without the use of mitomycin C. J Glaucoma. 2004;13:228–32.
34. Schotthoefer EO, Yanovitch TL, Freedman SF. Aqueous drainage device surgery in refractory pediatric glaucomas: I. Long-term outcomes. J AAPOS. 2008;12:33–9.
35. Schotthoefer EO, Yanovitch TL, Freedman SF. Aqueous drainage device surgery in refractory pediatric glaucoma: II. Ocular motility consequences. J AAPOS. 2008;12:40–5.
36. Susanna R, Oltrogge ED, Caran JC, Nicolela MT. Mitomycin as adjunct chemotherapy with trabeculectomy in congenital and developmental glaucomas. J Glaucoma. 1995;4:151–7.
37. Tixier J, Dureau P, Becquet F, et al. Deep sclerectomy in congenital glaucoma. Preliminary results. J Fr Ophthalmol. 1999;22:545–8.
38. Topouzis F, Coleman A, Choplin N, et al. Follow-up of the original cohort with the Ahmed glaucoma valve implant. Am J Ophthalmol. 1999;128:198–204.
39. Tung I, Marcus I, Thiamthat W, Freedman SF. Second glaucoma drainage devices in refractory pediatric glaucoma: failure by fibrovascular ingrowth. Am J Ophthalmol. 2014;158:113–7.
40. Waheed S, Ritterband DC, Greenfield DS, et al. Bleb-related ocular infection in children after trabeculectomy with mitomycin-C. Ophthalmology. 1997;1042:117–20.
41. Wallace DK, Plager DA, Snyder SK, et al. Surgical results of secondary glaucomas in childhood. Ophthalmology. 1998;105:101–11.
42. Wells AP, Cordeiro MF, Bunce C, Khaw PT. Cystic bleb formation and related complications in limbus-versus fornix based conjunctival flaps in pediatric and young adult trabeculectomy with mitomycin C. Ophthalmology. 2003;110:2192–7.
43. Whiteside-Michel J, Liebmann JM, Ritch R. Initial 5-fluorouracil trabeculectomy in young patients. Ophthalmology. 1992;99:7–13.

Angle-Closure Glaucoma: Risk Factors

54

Xinxing Guo and Mingguang He

Core Messages

- Acute angle-closure (AAC) is a relatively uncommon event, even in high risk populations, and it is difficult to predict who will suffer an AAC attack.
- Certain anatomic, genetic, and demographic factors increase the risk of AAC.
- Various systemic medications that induce mydriasis may trigger AAC attacks.
- An iridotomy significantly decreases the risk of AAC when the mechanism of closure is pupillary block.

54.1 Who Is at Risk for Acute Angle-Closure?

Demographic characteristics, ocular anatomy, genetic, and some external factors are all identified as risk factors for acute angle-closure (AAC). The majority of identified risk factors to date come from cross-sectional studies or clinical observations. Current on-going observational studies with long-term follow-up in narrow angle subjects may provide systematic longitudinal data for a better understanding of the natural history of the disease and risk factors in the future.

54.1.1 What Are the Anatomical Risk Factors?

Cross-sectional and clinical studies consistently find that small eyes with shallow anterior chambers, short axial lengths, small corneal diameters, shallow limbal chamber depths, and thick, relatively anteriorly positioned lenses are at risk for angle-closure [1]. Novel parameters recently established with anterior segment imaging include smaller anterior chamber width, area, and volume, thicker iris with greater curvature, and increased lens vault [2–4]. Acute elevation of intraocular pressure (IOP) in angle-closure is likely due to extensive pretrabecular obstruction by the peripheral iris. The proximity of the peripheral iris to the trabecular meshwork is considered a precondition for developing primary

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angle-closure. Therefore, the width of the angle is a commonly used parameter to grade or quantify the risk of angle-closure.

Gonioscopic examination remains the most important method for grading angle width and for describing other signs of angle-closure. Several gonioscopic grading methods have been devised, which include the Scheie, Shaffer, and Spaeth systems [5]. Each of these systems is based on the estimation of angle width in degrees or the visibility of angle landmarks. Gonioscopic grading is a subjective measurement that usually depends on the examiner's experience and skill. Anterior imaging or biometric technologies, such as ultrasound biomicroscopy (UBM), A-scan ultrasound biometry, IOLMaster, scanning peripheral anterior chamber depth analyzer (SPAC), and anterior segment optical coherence tomography (ASOCT), all provide objective means for quantifying the angle. Recent studies with ASOCT imaging revealed dynamic parameters such as changes in iris volume with dilation and choroidal expansion/effusion to be independent risk factors for angle-closure [6, 7]. SPAC, IOLMaster, and ASOCT are fast, noncontact methods of measurement and therefore may be more suitable for large-scale screening.

A simple dichotomous classification of angle width has been used in epidemiological studies, in which angles have been termed "occludable" or "not occludable" based on the number of quadrants (normally two or three quadrants) with posterior trabecular meshwork being not visible [8]. Although it is not directly relevant to AAC, cross-sectional studies suggest a "dose-response" increase in the rate of chronic angle-closure in eyes with narrower drainage angles [9]. Case-control studies consistently report that AAC eyes have a shorter axial length and shallower anterior chamber [10].

54.1.2 Age, Gender, and Ethnicity

AAC is rare before the age of 40 years. Studies consistently report that the anterior chamber depth (ACD) increases between 7 and 15 years of age and then decreases with increasing age [11]. The decrease in ACD in older individuals likely is due to the thickening and anterior movement of the lens primarily, resulting in increased prevalence of angle-closure with age [12, 13].

Female gender is a major predisposing factor for ACG development. The prevalence of all categories of angle-closure is two to five times higher in women than in men. This increased prevalence is likely due to shallower anterior chambers in women. A cross-sectional study in an adult Chinese population documented that older and female adults have narrower anterior chamber angles on gonioscopy [9].

Ethnic differences have been well-recognized in angle-closure. Both prevalence and incidence data demonstrate that angle-closure is most prevalent in the Inuit population of Alaska, and that it affects East Asian people more frequently than European or African people [14–16]. This ethnic difference may be attributed to differences in anatomy of the anterior chamber and angle. The majority of evidence suggests there is an inverse association between ACD and the rate of angle-closure in various ethnic groups: shallower ACDs are normally found in populations with higher rates of angle-closure.

54.1.3 Family History and Genetic Susceptibility

A positive family history has long been recognized as predisposing to angle-closure [17]. The similarities of ocular biometry in first-degree relatives with angle-closure indicate that angle-closure-related anatomical characteristics are heritable. The risk of developing angle closure glaucoma was reported to be 3.5 times higher in first-degree relatives of affected Inuit patients [18]. In particular, siblings of angle-closure patients were 7 times and nearly 14 times more likely to have narrow angles than the general population in Singapore and India, respectively [19, 20]. An investigation of Chinese twins confirms that the heritability of ACD and drainage angle width could be as high as 70–90 % [21]. A large number of studies

have investigated genetic determinants for angle-closure risk factors, while three genomic loci that predispose patients to angle-closure were recently identified by an extensive genome-wide association study: rs11024102 on PLEKHA7, rs3753841 on COL11A1, and rs1015213 on chromosome 8q [22].

Summary for the Clinician

- A narrow drainage angle is the primary anatomical risk factor for acute angle closure.
- The narrower the drainage angle, the greater the risk for developing angle closure.
- People aged 40 years and over, women, East Asians, and those with a positive family history are at higher risk for developing acute angle closure.
- Gonioscopy is an important diagnostic tool to identify people at risk; other anterior imaging or biometric technologies are more objective and reproducible and may be useful for screening.

54.2 Can I Predict Who Will Have an Angle-Closure Attack?

The incidence of AAC is approximately 5–11 per 100,000 per year in Chinese populations and is substantially lower in individuals of European ancestry [23]. Given that AAC is very uncommon even in high-risk populations, it remains challenging to predict or identify people who will develop AAC. It is not well-understood what causes eyes with narrow angles to develop AAC, given that good natural history data is not available.

No clinical test accurately predicts who will go on to develop an acute attack. Narrow angle width is recognized as the anatomical basis of angle-closure. Longitudinal data suggest that the rate of progression from narrow angles to established angle-closure (including AAC and other forms of angle-closure) is around 15 % over 10 years in Eskimos [24], 22 % over 5 years in Indians [25], and 6 % over a mean of 2.7 years in Caucasians [26]. The data presented from these studies [24–26] has its limitations, so the true rate of angle-closure development is uncertain. Furthermore, these studies identified angle-closure as an endpoint, not glaucoma, so it is unclear how many of these individuals would eventually have developed glaucoma. Most persons with narrow angles will not develop glaucomatous damage even over a long period of time. Unfortunately, these longitudinal studies did not identify any anatomical characteristics as good predictors for the glaucomatous damage from angle-closure. Of note, the on-going Zhongshan Angle-closure Prevention (ZAP) trial aims to evaluate the long-term effectiveness of prophylactic LPI and determine the natural history of angle-closure glaucoma and its risk factors [27].

Appositional closure is commonly cited as an indication for prophylactic treatment, although this is not backed by evidence in the literature [28, 29]. Appositional closure is a reversible, temporary contact between the peripheral iris and trabecular meshwork at a location anterior to the pigmented trabecular meshwork. It can usually be confirmed by gonioscopy. If the apposition cannot be opened by indentation gonioscopy, it is then classified as peripheral anterior synechiae (PAS). Anterior segment imaging systems, such as ultrasound biomicrscopy (UBM) or ASOCT, are able to identify contact between the iris and the trabecular meshwork, but may not be able to differentiate whether it is appositional or synechial contact. Evidence supporting the fact that appositional closure is pathologic comes from a histological study [30]. By looking at donated eyes, a study in India reported that pathological changes of the trabecular meshwork developed not only in areas with peripheral synechiae, but also in those with appositional closure, although these findings have not yet been replicated.

Dynamic physiologic factors may also contribute to the development of AAC. One case-control study using UBM found that the (fellow) eyes of persons experiencing an AAC attack responded

differently to provocative testing than normal controls [31]. This finding has yet to be replicated; however, with the development of anterior imaging techniques, physiologic factors such as iris dynamics and choroidal effusion dynamic are candidates for predicting future AAC.

Some investigators have used provocative tests to identify at-risk individuals. These tests simulate the physiological conditions under which angle-closure may develop. Nearly ten different provocative tests have been proposed, but the most common one is the dark room prone provocative test. Placing the patient face down in a dark room is supposed to increase the amount of relative pupillary block resulting from forward movement of the lens relative to the iris. An IOP rise of more than 8 mmHg 1 h after the test is considered positive [32]. A UBM dark room provocative test may have greater sensitivity to identify eyes that are at high risk [33]. However, none of these provocative tests has been shown to be truly predictive of developing angle-closure glaucoma or AAC. In fact, Lowe and Wilensky have both asserted that provocative tests are probably poor predictors of future risk based on their research [26, 34]. Given the effort and potential risk of performing the provocative tests and the lack of proven benefit, most practitioners in the West do not perform these tests as part of the clinical evaluation. More evidence from longitudinal data is needed to determine if these tests have a place in clinical practice.

Summary for the Clinician

- It is challenging to predict who will develop AAC due to the lack of longitudinal data for at-risk individuals.
- Appositional closure, confirmed by gonioscopy, is a sign of increased risk and may warrant prophylactic treatment (although data are insufficient to make a definitive recommendation).
- Provocative tests might be of value, but more research is needed.

54.3 What Systemic Medications Must Narrow Angle Patients Be Counseled Against Using? Is It Safe to Use These Medications if There Is a Patent LPI?

Systemic medications may precipitate AAC in people with preexisting narrow anterior chamber angles. Adrenergic and anticholinergic agents can induce acute attacks by causing mydriasis and increasing pupillary block. Medications for nausea, bladder control, and psychiatric conditions have anticholinergic activity. Over-the-counter cold medications may have α-adrenergic activity. Systemic (or nasal) administration of epinephrine (including adrenaline) used for general anesthesia or nasal diseases [35] and β_2 adrenergic agents (commonly used for asthma or chronic obstructive pulmonary disease, e.g., salbutamol) have caused acute or intermittent angle-closure [36]. Some drugs with indirect sympathomimetic activities, such as amphetamines and certain antidepressant agents, may also induce AAC [37]. Anticholinergic agents (such as atropine and scopolamine) that are widely used in general anesthesia, cardiac, and gastrointestinal diseases are well-known precipitating agents for AAC. These drugs often have a long-acting mydriatic effect and also cause relaxation of the ciliary muscle [38]. Even botulinum toxin inhibits acetylcholine release and has been reported to cause AAC after being injected around the eyes for blepharospasm [39]. The use of any of these medications should be discussed with patients diagnosed with narrow angles.

Sulfa-based drugs (i.e., topiramate, for epilepsy treatment; acetazolamide, for ocular hypotensive treatment) have also been identified as causing AAC, although this is relatively uncommon and not through a pupillary block mechanism [40]. Ciliochoroidal effusions caused by the medication rotate the ciliary body and lens forward. Ultrasound imaging has confirmed that edema and anterior rotation of ciliary body, choroidal detachment, and supraciliary effusion are present in some of these cases. Patients with open angles are also at risk for angle-closure from this mechanism.

Laser peripheral iridotomy (LPI) remains the cornerstone of prophylactic management of pupillary block angle-closure. In the narrow angle caused by a pupil block mechanism, LPI is able to equilibrate the pressure between the two chambers, allowing the peripheral iris to fall backwards resulting in a wider angle configuration. In these cases, LPI is able to significantly reduce the risk of angle-closure, so much so that systemic medications with a mydriatic effect can be used safely. However, in eyes that have angle-closure due to nonpupil block mechanisms (such as plateau iris and peripheral iris thickening), even with a patent PI, dilation may still exacerbate the crowding of the iris in the angle recess, and therefore, could theoretically induce AAC.

Summary for the Clinician

- Systemic drugs with mydriatic effects can precipitate AAC in eyes with narrow angles.
- Use of systemic drugs with adrenergic and anticholinergic effects can be used after LPI if pupillary block is the only mechanism of angle closure. Routine gonioscopy should still be performed.
- Use of systemic drugs that cause mydriasis should be avoided in narrow angles due to plateau iris syndrome or peripheral iris thickening even if there is a patent LPI.

54.4 Which Patients Without Appositional Closure Deserve a Laser Iridotomy?

Laser iridotomy, more specifically Nd:YAG laser iridotomy, is indicated if there is acute angle closure and is the only prophylactic treatment for angle-closure. It eliminates the risk of acute attack by balancing the pressure between the anterior and posterior chambers, thus relieving pupillary block. It can be performed successfully in most eyes within a few minutes with minimal complications, such as occasional bleeding from the iridotomy site, an acute rise in IOP in about 10 % of eyes, and mild iritis [41].

The fellow eyes of individuals who have suffered a one-eyed AAC attack are at the highest risk of developing an AAC attack. Early studies of such patients indicate that nearly half will develop an acute attack within approximately 5 years [42, 43]. In fact, 10 % of all attacks are bilateral [44]. Such people should therefore undergo prophylactic laser iridotomy as soon as possible. Similarly, people with milder episodes (based on history and clinical signs of previous angle-closure) are also considered high risk, especially if there is evidence of a transient elevation in IOP.

Laser iridotomy also is considered in conditions with an underlying mechanism of secondary pupillary block, such as uveitic glaucoma, aphakic pupillary block after fill with silicone oil or gas, pseudophakic pupillary block in cases with anterior chamber intraocular lens (IOL), posterior chamber IOL, etc. It has been suggested by early studies that LPI also is helpful in pigment dispersion syndrome (PDS) with 'reverse pupillary block'. Backward bowing of the iris results in rubbing of the iris pigment epithelium against the lens zonules, leading to the dispersion of pigment granules that disrupt flow through the trabecular meshwork. Although the effectiveness of laser iridotomy in PDS is under debate, a recent randomized controlled trial indicated that the procedure reduced the rate of IOP elevation in high-risk eyes to the same level as the low-risk eyes at the end of 10-year follow-up [45].

Summary for the Clinician

- Laser iridotomy relieves pupillary block.
- Fellow eyes of patients suffering an acute angle closure attack are considered to be at the highest risk for attack and should be treated as soon as possible.
- Conditions with secondary pupillary block are also indications for iridotomy, while its effectiveness in PDS is yet to be further studied.

References

1. Lowe RF. Primary angle-closure glaucoma: a review of ocular biometry. Aust J Ophthalmol. 1977;5:9–17.
2. Nongpiur ME, Sakata LM, Friedman DS, et al. Novel association of smaller anterior chamber width with angle closure in Singaporeans. Ophthalmology. 2010;117:1967–73.
3. Wang B, Sakata LM, Friedman DS, et al. Quantitative iris parameters and association with narrow angles. Ophthalmology. 2010;117:11–7.
4. Wu RY, Nongpiur ME, He MG, et al. Association of narrow angles with anterior chamber area and volume measured with anterior-segment optical coherence tomography. Arch Ophthalmol. 2011;129:569–74.
5. Spaeth GL, Aruajo S, Azuara A. Comparison of the configuration of the human anterior chamber angle, as determined by the spaeth gonioscopic grading system and ultrasound biomicroscopy. Trans Am Ophthalmol Soc. 1995;93:337–47.
6. Kumar RS, Quek D, Lee KY, et al. Confirmation of the presence of uveal effusion in Asian eyes with primary angle closure glaucoma: an ultrasound biomicroscopy study. Arch Ophthalmol. 2008;126:1647–51.
7. Aptel F, Denis P. Optical coherence tomography quantitative analysis of iris volume changes after pharmacologic mydriasis. Ophthalmology. 2010;117:3–10.
8. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002;86:238–42.
9. He M, Foster PJ, Ge J, et al. Gonioscopy in adult Chinese: the Liwan Eye Study. Invest Ophthalmol Vis Sci. 2006;47:4772–9.
10. Sihota R, Lakshmaiah NC, Agarwal HC, Pandey RM, Titiyal JS. Ocular parameters in the subgroups of angle-closure glaucoma. Clin Exp Ophthalmol. 2000;28:253–8.
11. Alsbirk PH. Anterior chamber depth in Greenland Eskimos. I. A population study of variation with age and sex. Acta Ophthalmol. 1974;52:551–64.
12. Lowe RF. Anterior lens displacement with age. Br J Ophthalmol. 1970;54:117–21.
13. Lowe RF. Aetiology of the anatomical basis for primary -closure glaucoma. Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. Br J Ophthalmol. 1970;54:161–9.
14. He M, Foster PJ, Johnson GJ, Khaw PT. Angle-closure glaucoma in East Asian and European people. Different diseases? Eye. 2006;20:3–12.
15. Arkell SM, Lightman DA, Sommer A, et al. The prevalence of glaucoma among Eskimos of northwest Alaska. Arch Ophthalmol. 1987;105:482–5.
16. Tielsch JM, Katz J, Singh K, et al. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. Am J Epidemiol. 1991;134:1102–10.
17. Lowe RF. Primary angle-closure glaucoma. Inheritance and environment. Br J Ophthalmol. 1972;56:13–20.
18. Alsbirk PH. Primary angle-closure glaucoma. Oculometry, epidemiology, and genetics in a high risk population. Acta Ophthalmol. 1976;54:5–31.
19. Amerasinghe N, Zhang J, Thalamuthu A, et al. The heritability and sibling risk of angle closure in Asians. Ophthalmology. 2011;118:480–5.
20. Kavitha S, Zebardast N, Palaniswamy K, et al. Family history is a strong risk factor for prevalent angle closure in a South Indian population. Ophthalmology. 2014;121:2091–7.
21. He M, Wang D, Zheng Y, et al. Heritability of anterior chamber depth as an intermediate phenotype of angle-closure in Chinese: the Guangzhou Twin Eye Study. Invest Ophthalmol Vis Sci. 2008;49:81–6.
22. Vithana EN, Khor CC, Qiao C, et al. Genome-wide association analyses identify three new susceptibility loci for primary angle closure glaucoma. Nat Genet. 2012;44:1142–6.
23. Seah SK, Foster PJ, Chew PT, et al. Incidence of acute primary angle-closure glaucoma in Singapore. An island-wide survey. Arch Ophthalmol. 1997;115:1436–40.
24. Alsbirk PH. Anatomical risk factors in primary angle-closure glaucoma. A ten year follow up survey based on limbal and axial anterior chamber depths in a high risk population. Int Ophthalmol. 1992;16:265–72.
25. Thomas R, George R, Parikh R, Muliyil J, Jacob A. Five year risk of progression of primary angle-closure suspects to primary angle-closure: a population based study. Br J Ophthalmol. 2003;87:450–4.
26. Wilensky JT, Kaufman PL, Frohlichstein D, et al. Follow-up of angle-closure glaucoma suspects. Am J Ophthalmol. 1993;115:338–46.
27. Jiang Y, Friedman DS, He M, et al. Design and methodology of a randomized controlled trial of laser iridotomy for the prevention of angle closure in southern China: the Zhongshan angle Closure Prevention trial. Ophthalmic Epidemiol. 2010;17:321–32.
28. Ritch R. Definitive signs and gonioscopic visualization of appositional angle-closure are indications for prophylactic laser iridectomy. Surv Ophthalmol. 1996;41:33–6.
29. Rivera AH, Brown RH, Anderson DR. Laser iridotomy vs surgical iridectomy. Have the indications changed? Arch Ophthalmol. 1985;103:1350–4.
30. Sihota R, Lakshmaiah NC, Walia KB, et al. The trabecular meshwork in acute and chronic angle-closure glaucoma. Indian J Ophthalmol. 2001;49:255–9.
31. Friedman DS, Gazzard G, Foster P, et al. Ultrasonographic biomicroscopy, scheimpflug photography, and novel provocative tests in contralateral eyes of Chinese patients initially seen with acute angle -closure. Arch Ophthalmol. 2003;121:633–42.
32. Hyams SW, Friedman Z, Neumann E. Elevated intraocular pressure in the prone position. A new provocative test for angle-closure glaucoma. Am J Ophthalmol. 1968;66:661–72.
33. Ishikawa H, Esaki K, Liebmann JM, Uji Y, Ritch R. Ultrasound biomicroscopy dark room provocative testing: a quantitative method for estimating anterior

chamber angle width. Jpn J Ophthalmol. 1999;43: 526–34.
34. Lowe RF. Primary angle-closure glaucoma. A review of provocative tests. Br J Ophthalmol. 1967;51:727–32.
35. Zenzen CT, Eliott D, Balok EM, Watnick RL, German P. Acute angle-closure glaucoma associated with intranasal phenylephrine to treat epistaxis. Arch Ophthalmol. 2004;122:655–6.
36. Shah P, Dhurjon L, Metcalfe T, Gibson JM. Acute angle-closure glaucoma associated with nebulised ipratropium bromide and salbutamol. Br Med J. 1992;304:40–1.
37. Kinek M. Glaucoma following the antidepressant mianserin. Harefuah. 1990;118:699–700.
38. Tripathi RC, Tripathi BJ, Haggerty C. Drug-induced glaucomas: mechanism and management. Drug Saf. 2003;26:749–67.
39. Corridan P, Nightinglae S, Mashoudi N, Williams AC. Acute angle-closure glaucoma following botulinum toxin injection for blepharospasm. Br J Ophthalmol. 1990;74:309–10.
40. Bhattacharyya KB, Basu S. Acute myopia induced by topiramate: report of a case and review of the literature. Neurol India. 2005;53:108–9.
41. Wilensky JT, Ritch R, Kolker AE. Should patients with anatomically narrow angles have prophylactic iridectomy? Surv Ophthalmol. 1996;41:31–6.
42. Lowe RF. Acute angle-closure glaucoma the second eye: an analyses of 200 cases. Br J Ophthalmol. 1962;46:641–50.
43. Snow JT. Value of prophylactic peripheral iridectomy on the second eye in angle-closure glaucoma. Trans Ophthalmol Soc U K. 1977;97:189–91.
44. Lee JW, Wong BK, Yick DW, et al. Primary acute angle closure: long-term clinical outcomes over a 10-year period in the Chinese population. Int Ophthalmol. 2014;34:165–9.
45. Gandolfi SA, Ungaro N, Tardini MG, et al. A 10-year follow-up to determine the effect of YAG laser iridotomy on the natural history of pigment dispersion syndrome: a randomized clinical trial. JAMA Ophthalmol. 2014;132:1433–8.

Angle-Closure Glaucoma: Iridotomy

55

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Core Messages

- When performing peripheral laser iridotomy, different laser settings and laser sources may be necessary depending on iris color and thickness.
- If it is difficult to penetrate the iris to complete an iridotomy, various adjustments can be made to laser settings.
- Complications of laser iridotomy vary from transient to long-term.
- A surgical iridectomy is always an option if laser iridotomy is not possible.

55.1 What Pre-treatment Is Needed Before LPI?

To avoid transient intraocular pressure (IOP) elevation, 1 % apraclonidine hydrochloride ophthalmic solution should be administered 1 h before LPI. Brimonidine 0.15–0.2 % has also been reported to be effective in preventing a transient IOP elevation associated with LPI [1, 2]. The more dilated a pupil is, the thicker the iris stroma will be and the higher the laser power necessary to complete the LPI. Therefore, the pupil should be maximally constricted before the procedure. For this purpose, 1–2 % pilocarpine ophthalmic solution should be administered 30 min to 1 h before the procedure is started. Shining a bright light in the fellow eye during the procedure will also accomplish pupil constriction by the consensual light reflex. IOP should be controlled as much as possible before the procedure. Steroid ophthalmic solution should be administered if there is inflammation in the anterior chamber.

55.2 What Settings Should Be Used to Perform LPI?

55.2.1 Settings for Argon LPI

An LPI-specific laser contact lens, such as the Abraham lens, that has a high power plus segment should be used. This lens helps to concentrate the laser energy onto the iris and prevents stray energy from reaching the posterior segment after penetration. In general, argon LPI is performed in two steps (Table 55.1). The purpose of the first step is to contract iris tissue. The purpose of the second step is to penetrate the iris and cleanup the LPI. In general, the first step employs a larger spot size, longer duration, and lower power, while the second step employs a smaller spot size, shorter duration, and higher power. Once penetration is confirmed in the second step, for final touch-up of

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Table 55.1 Basic settings for argon laser peripheral iridotomy

	Abraham	
Contact lens	First step	Second step
Spot size (μm)	200–500	50
Duration (s)	0.2–0.5	0.02–0.05
Power (mW)	200–400	1000
Recommended maximum shot number	5	300

the iridotomy the laser settings can be changed to a longer duration and lower power.

55.2.2 Settings for Nd-YAG LPI

One should again use a lens compatible with the Nd-YAG laser. An Abraham iridotomy lens works well. Laser power for Nd-YAG LPI varies depending on the particular laser used. One should refer to the laser's manual to confirm the appropriate power. In general, the number of pulses is between 1 and 4 and laser power ranges from 1 to 10 mJ per burst. Low laser power and a single pulse per unit burst are recommended. Nd-YAG laser sometimes results in bleeding from the LPI site. Before Nd-YAG LPI, pretreatment with an argon laser is useful to avoid this complication [3] because the argon laser coagulates blood vessels. The settings for this step are the same as the settings for the first step of an argon-only LPI (Table 55.1). After argon pretreatment, Nd-YAG is used to penetrate the iris. Usually less YAG energy is necessary in the combined Argon/YAG LPI [3].

Summary for the Clinician

- Settings for an argon-only laser iridotomy are listed in Table 55.1.
- Settings for a Nd:YAG laser iridotomy can vary from 1 to 10 mJ per burst (usually 3.5–8 mJ is used) and 1 pulse per unit burst is recommended.
- In a combined argon/YAG iridotomy, less YAG energy is needed for penetration after adequate argon pretreatment.
- Pilocarpine 1–2 % should be given preoperatively to maximally constrict the pupil and stretch the iris. Intraocular pressure elevation can be prevented with apraclonidine hydrochloride 1 % or brimonidine 0.15–0.2 % given preoperatively.
- Topical steroids should be used postoperatively to control inflammation.

55.3 How Does Iris Color Affect the Laser Settings?

Iris thickness varies by race. Medium brown irides are relatively easy to penetrate with argon laser alone, while light blue and dark brown irides become more difficult cases on the argon laser. The argon laser is more easily absorbed by brown irides than by blue irides because of the increased pigment. Higher energy must be used in blue irides. In very dark irides, charring of the tissue is more frequent. Charring makes final penetration of the iris difficult to impossible. One should apply lower laser power of longer duration and use a larger spot size to minimize the chances of charring a very dark iris.

In the case of a pure Nd-YAG LPI, the procedure is much more easily performed on lighter irides than in those that are very dark and/or very thick. In the latter, it takes many more pulses to penetrate and bleeding can be a significant problem during the procedure.

Summary for the Clinician

- Thick irides will require higher argon laser energy, but this may also induce charring that can make penetration difficult with argon laser.
- For a thick, dark iris, a combined argon/YAG iridotomy may be best procedure where the argon laser thins the iris and coagulates blood vessels and the YAG laser makes the final penetration.
- Blue irides may be most easily penetrated by the Nd:YAG laser alone.

Table 55.2 Reasons for difficulty with LPI and recommended adjustments

Reason	Corresponding adjustment
Low visibility of iris	Change of laser site
	Surgical iridectomy
Thick iris	Apply miotics
	Change of laser site
	Surgical iridectomy
Blue iris	Change of laser source
Severe inflammation in the anterior chamber	Apply steroid ophthalmic solution
	Medicate and wait
	Surgical iridectomy
Low laser power concentration	Use adequate contact lens
Hemorrhage in the anterior chamber	Change of laser site
Air bubble	Application of gentle pressure
	Avoid laser at the 12 o'clock position

55.4 If It Is Difficult to Penetrate the Iris, What Adjustments Can Be Made to the Laser Settings?

The possible reasons for difficulty in penetrating iris and the corresponding adjustments are summarized in Table 55.2. Laser power should be concentrated on the targeted iris; otherwise, the number of laser-related complications may increase.

If iris penetration fails, do not continue using the current laser settings without making adjustments. If one applies too much laser power while performing LPI, severe complications, such as large IOP spikes, corneal endothelial decompensation, lens opacity, and inflammation, may be induced. If one notes these complications during a procedure, the laser procedure should be terminated. When one notices corneal opacity and edema, or if there is inflammation in the anterior chamber, appropriate antiinflammatory therapy should be instituted postoperatively. A dilated pupil or arcus senilis can sometimes make it difficult to create an LPI. If difficulty arises, one should seek a more suitable site for LPI or choose to do a surgical iridectomy instead.

Summary for the Clinician

- If difficulty arises in iris penetration, laser settings can be adjusted, and the iris target site can be changed, or a surgical iridectomy may be contemplated.
- If intraocular damage is witnessed from high laser energy, one should stop the procedure and adjust settings.

55.5 What Potential Complications Should Be Anticipated with Laser Peripheral Iridotomy and How Should Each One Be Managed?

55.5.1 Visual Discomfort

Patients sometimes complain of visual disturbances after LPI. Several factors may be related to this complaint, including anterior segment inflammation, anterior chamber pigment, disturbance of the pupillary light reflex, and a change in refractive error. In many cases, this complaint is transient and will disappear after a short time.

55.5.2 Diplopia and/or Glare

Occasionally, patients complain of monocular diplopia, glare, or a second image, usually described as a line or streak from oncoming lights after LPI. It is hypothesized that the tear meniscus at the lid margin acts as a prism deflecting light into the iridotomy. Although this complication sometimes disappears within several months after LPI, wearing sunglasses or colored contact lenses that cover the LPI site may ameliorate this symptom.

55.5.3 Hemorrhage

The rate of hemorrhage with argon laser is very low, while that with Nd-YAG laser is relatively high. Although generally this complication is not severe, one should consider performing argon laser pretreatment prior to Nd-YAG LPI to prevent it. The settings for this preliminary procedure are the same as those for the first step of an argon LPI. If bleeding develops during the procedure, the iridotomy lens can be firmly pressed against the eye to help stop the hemorrhage. Argon laser, if available, can help coagulate a bleeding vessel. If the hemorrhage is significant, it may increase IOP, so a postoperative IOP check is particularly important.

55.5.4 Corneal Damage

There are a few papers reporting LPI as the inciting etiology for corneal endothelial decompensation in Japan [4, 5] (see Chap. 48). In Asian countries, penetrating keratoplasty has become necessary for cases of LPI-related bullous keratopathy [4–6]. Specular microscopy can be performed prior to LPI to follow endothelial cell counts. Since a Nd-YAG laser has been reported to be less damaging to the corneal endothelium than an argon laser [7], it may be better to use Nd-YAG laser for LPI, particularly in eyes presenting with low endothelial cell counts.

There are two types of corneal damage that can be suffered from LPI. The first type develops immediately after LPI. Application of high laser power in the setting of a shallow anterior chamber is one situation where this damage can occur. The second type is delayed by years. Laser-induced thermal damage of the cells is one explanation. Other possible explanations are that a jet of aqueous humor streams through the small iridotomy opening causing shear stress to cells [8], or that there is a release of chemicals from activated macrophages [9].

55.5.5 Lens Damage

Argon LPI sometimes results in subcapsular opacity, although this opacity is rare [7]. Nd-YAG LPI has also been reported to cause lens damage and rupture of the capsule [10]. If a cataract develops, one can observe it until it becomes visually significant. If the lens capsule is ruptured, one should look for signs of inflammation.

55.5.6 IOP Elevation

The degree of IOP elevation induced by LPI depends on total laser power and is transient in most cases. Pretreatment with an alpha-blocker should suppress laser-induced acute IOP elevation. One should routinely measure IOP 1 h following laser iridotomy so as to catch the occasional patient who will have an IOP spike despite alpha-blocker pretreatment. These spikes are treated with topical and systemic hypotensive medications. Rarely, these IOP spikes will not resolve with medical treatment and surgical intervention may become necessary.

55.5.7 Progression of PAS Formation

LPI successfully deepens the anterior chamber, but some cases show progression of PAS formation, particularly in eyes with acute angle-closure. In a study with 3 years of follow-up, PAS were more likely to progress in eyes with plateau iris syndrome or in those eyes whose IOP was unresponsive to medical therapy prior to LPI [11]. Lens extraction may be effective to suppress further PAS formation.

55.5.8 Posterior Synechia

Insufficient administration of topical steroid sometimes results in posterior synechia after LPI treatment. Continuous administration of pilocarpine ophthalmic solution long after LPI may also lead to the development of posterior synechia. One should stop administration of pilocarpine after LPI.

55.5.9 LPI Closure

It is not uncommon to encounter LPI closure during follow-up. LPI closure is much more

commonly observed in eyes with secondary angle-closure, such as that due to uveitis or neovascular glaucoma, and after argon-only LPI. One can repeat LPI for these eyes, but one should consider surgical iridectomy if there are significant signs of anterior chamber inflammation.

Summary for the Clinician

- Complications of LPI include visual discomfort, unwanted visual phenomena, hemorrhage, corneal damage, lens damage, IOP elevation, progression of peripheral anterior synechia, posterior synechia, and LPI closure.

55.6 Under What Circumstances Is Surgical Iridectomy Indicated?

Surgical iridectomy is recommended if it becomes impossible to perform an adequate laser iridotomy (see Table 55.3). Surgical iridectomy is usually performed at a superior-temporal or superior-nasal location. If the eye is filled with silicone oil, then the iridectomy should be placed inferiorly since silicone oil rises and may block a patent superior iridectomy. Both LPI and surgical iridectomy are ineffective in eyes with synechial angle-closure in terms of helping to lower IOP or prevent further angle-closure. Goniosynechialysis or trabeculectomy can be tried in these eyes.

Table 55.3 Indications for surgical iridectomy

Severe damage of corneal endothelium
Low visibility of iris tissue due to corneal edema, very thick and/or dilated irides, and other reasons
Extremely shallow anterior chamber
Eyes with secondary angle-closure glaucoma that have a high possibility of LPI closure

55.7 How Should a Surgical Iridectomy Be Performed?

Before taking the patient into the operating room, 1–2 % pilocarpine ophthalmic solution is administered. A scleral incision 3-mm in length should be made parallel to the limbus at the gray line. Iris tissue may prolapse from the wound. This prolapsed iris tissue is excised and the remaining iris tissue is gently massaged back into the eye. If iris tissue does not spontaneously prolapse, Colibri forceps can be used to pull iris out through the wound (similar to what one would do when performing an iridectomy as part of a trabeculectomy). Finally, the scleral wound is sutured. Major complications include incomplete iridectomy, hyphema, shallow or flat anterior chamber, cataract formation, transient IOP elevation, posterior synechiae, pupil distortion, infection, and malignant glaucoma.

Summary for the Clinician

- Surgical iridectomy is less commonly performed today due to its invasive nature but can be a successful alternative to laser iridotomy.
- Surgical iridectomies should be placed superiorly unless there is silicone oil in the eye and then they should be placed inferiorly.
- Iridectomies are not expected to lower IOP in eyes with synechial angle-closure.

References

1. Chen TC. Brimonidine 0.15% versus apraclonidine 0.5% for prevention of intraocular pressure elevation after anterior segment laser surgery. J Cataract Refract Surg. 2005;21:1707–12.
2. Yuen NS, Cheung P, Hui SP. Comparing brimonidine 0.2% to apraclonidine 1.0% in the prevention of intraocular pressure elevation and their papillary effects following laser peripheral iridotomy. Jpn J Ophthalmol. 2005;49:89–92.

3. Ang LP, Higashihara H, Sotozono C, et al. Argon laser iridotomy-induced bullous keratopathy a growing problem in Japan. Br J Ophthalmol. 2007;91:1613–5.
4. Shimazaki J, Amano S, Uno T, et al. National survey on bullous keratopathy in Japan. Cornea. 2007;26:274–8.
5. Kashiwagi K, Tsukahara S. Examination and treatment of patients with angle-closure glaucoma in Japan: results of a nationwide survey. Jpn J Ophthalmol. 2004;48:133–40.
6. Robin AL, Pollack IP. A comparison of neodymium: YAG and argon laser iridotomies. Ophthalmology. 1984;91:1011–6.
7. de Silva DJ, Gazzard G, Foster P. Laser iridotomy in dark irides. Br J Ophthalmol. 2007;91:222–5.
8. Yamamoto Y, Uno T, Shisida K, et al. Demonstration of aqueous streaming through a laser iridotomy window against the corneal endothelium. Arch Ophthalmol. 2006;124:387–93.
9. Kaji Y, Oshika T, Usui T, et al. Effect of shear stress on attachment of corneal endothelial cells in association with corneal endothelial cell loss after laser iridotomy. Cornea. 2005;24:S55–8.
10. Fernandez-Bahamonde JL. Iatrogenic lens rupture after a neodymium: yttrium aluminum garnet laser iridotomy attempt. Ann Ophthalmol. 1991;23:346–8.
11. Choi JS, Kim YY. Progression of peripheral anterior synechiae after laser iridotomy. Am J Ophthalmol. 2005;140:1125–7.

Angle-Closure Glaucoma: Imaging

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Core Messages

- Imaging devices provide an objective method for both qualitative and quantitative analysis of the anterior chamber angle (ACA).
- Ultrasound biomicroscopy (UBM) gives a two-dimensional image of the ACA, along with details of the ciliary body and iris, using high frequency ultrasound.
- Anterior segment optical coherence tomography (AS-OCT) provides cross-sectional images of the anterior chamber via low-coherence interferometry (infrared light). AS-OCT is noncontact and has higher resolution compared to UBM.
- Both devices have shown good potential as diagnostic tools in the detection and management of angle closure. There is good agreement between these devices and gonioscopy, the current reference standard for angle examination.
- The AS-OCT cannot image structures posterior to the iris, such as the ciliary body.
- Qualitative and quantitative analysis of the angle have shown moderate to good reproducibility with both devices.
- The scleral spur (SS) is an important landmark for UBM and AS-OCT images of the angle, from which quantitative measurements of the angle are made. While the SS remains the only detectable landmark on time domain OCT (TD-OCT), Schwalbe's line (SL) could be a potential new landmark when imaging is performed with spectral domain OCT (SD-OCT).

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56.1 Is New Imaging Technology Useful in Angle Examination?

Yes, new imaging devices are useful in angle examination; however, they have their individual limitations. Indirect gonioscopy is the current reference standard for visualizing the anterior chamber angle (ACA) of the eye. Gonioscopy is

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inexpensive, as it does not require sophisticated or supplementary equipment beyond a gonioscopy lens and slit-lamp. However, gonioscopy is a skill that is difficult to master and quantitative evaluation of the ACA is not possible with it. Gonioscopy is subjective. Previous studies have shown that there is only moderate agreement even between experienced examiners [1, 2]. Gonioscopy findings can be affected by room illumination, inadvertent pressure on the globe, and the direction of gaze. Another major limitation is the inability to visualize structures posterior to the iris, such as the ciliary body and ciliary processes.

The advent of new imaging techniques has allowed the ophthalmologist to objectively visualize the angle, as well as structures posterior to the iris that may affect the angle [3, 4]. These new technologies are able to perform objective measures of the ACA and provide a convenient way to document the angle's configuration. The two most widely used imaging devices are ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT). With ***UBM***, a two-dimensional view of the anterior chamber, including the angle and the iris, and structures posterior to the iris, including the ciliary body/processes and lens, are imaged [3, 4]. As the device uses sound waves, it can assess angle details when corneal pathology precludes anterior chamber visualization. On the other hand, ***AS-OCT*** uses infrared light to provide images of the angle and anterior chamber in real time. The advantages of AS-OCT are that it is noncontact and has higher scanning resolution than UBM. Additionally, with the aid of a built-in real-time charge-coupled device displaying the position of the scan line, imaging can be performed in the dark. Both devices allow for electronic storage of images that can be analyzed later, either qualitatively or quantitatively.

There are inherent limitations to each imaging technique. Both UBM and earlier time-domain (TD-OCT) capture only a single cross-section of the angle [4, 5], and thus, an observer can miss angle findings if imaging is not performed at exactly the location of angle pathology. The next generation spectral domain OCT (SD-OCT) improves resolution and reduces motion artifacts compared to earlier TD-OCT, while also providing two-dimensional, single cross-sectional imaging of the ACA. With the advent of swept source OCT (SS-OCT), which allows for Scheimpflug-like 360° angle imaging, the earlier limitations of AS-OCT may be potentially overcome, allowing the clinician to obtain an almost 'gonioscopic' view of the angle. Both UBM and the earlier TD-OCT devices rely on the scleral spur as a reference point, a landmark that lies approximately 250–500 μm posterior to the trabecular meshwork; however, it is not always possible to detect the scleral spur using these instruments [6, 7]. As the light source wavelength used in the newer SS-OCT devices is different, landmarks like the Schwalbe's line (SL) have been evaluated and quantified as a reference point. For any of the anterior segment OCTs, structures posterior to the iris cannot be imaged. Finally, both devices are costly.

Summary for the Clinician

- Gonioscopy is the reference standard for assessing the ACA, but it requires skill to perform and shows moderate inter-observer reproducibility.
- Imaging instruments such as UBM and AS-OCT offer an objective way to assess the angle and images can be stored electronically.
- Imaging tools allow both qualitative and quantitative analysis of angle images.
- Only one cross-section of the eye can be scanned at each time point using TD-OCT and SD-OCT instruments.
- SS-OCT allows for 360° imaging of the ACA providing a 'gonioscopic' view of the angles.

56.2 What Imaging Devices Are Currently Available to Examine the ACA?

Various imaging devices are currently available to visualize the ACA: UBM, Scheimpflug photography, and AS-OCT.

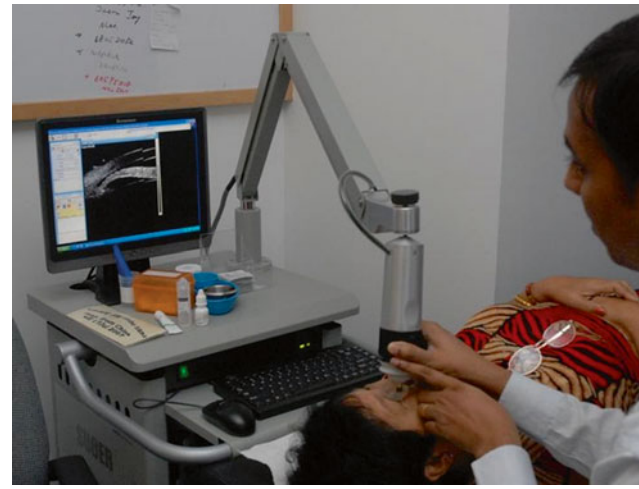

Fig. 56.1 UBM machine imaging a patient in the supine position

56.2.1 Ultrasound Biomicroscopy

Ultrasound biomicroscopy (UBM) is a high frequency ultrasound device (35–100 MHz) that allows detailed imaging of the ACA, including the pars plana and ciliary body (Fig. 56.1) [8]. It incorporates a high frequency transducer into a B-mode clinical scanner [6]. A 50 MHz transducer gives a lateral resolution of 50 μm and an axial resolution of 25 μm with tissue penetration of 5 mm. The scan rate may vary from 8 to 22 frames/s depending on the machine. A real time two-dimensional section of the eye that changes as the probe is moved is acquired on a screen. The images can be stored electronically or printed out. An immersion technique is required that involves the patient lying down with the ultrasound probe suspended from an articulated arm; the patient's eye needs to be anesthetized prior to insertion of a PMMA or silicone cup between the eyelids with a coupling medium placed in the cup. Earlier devices (UBM from Paradigm Medical Industries, Inc. Salt Lake City, UT, USA) could image only one quadrant of the eye at one time point. Newer devices with a 35 MHz probe (OTI, Ophthalmic Technologies, Toronto, Canada and VuMax II, Sonomed Inc., Lake Success, NY, USA) can acquire 180° of the eye in one frame. Both qualitative and quantitative analyses of images is currently possible using customized software.

56.2.2 Anterior Segment Optical Coherence Tomography

Optical coherence tomography (OCT) uses the principle of low coherence interferometry to obtain in-vivo cross-sectional images of tissues rapidly and without eye contact. To improve visualization of anterior segment structures, OCT technology has undergone several modifications. The wavelength of light used by the earlier time-domain AS-OCT devices was changed to 1310 nm (from 800 nm for posterior segment imaging) to provide increased penetration through light-scattering ocular structures, such as the sclera and the iris. This change results in more detailed visualization of angle morphology and reduces the amount of light reaching the retina [5, 9–11]. This technology permits image acquisition at a rate of 8 frames/s with a transverse resolution of 60 μm and an axial resolution of 10–20 μm. Furthermore, the use of wide-field scanning optics (16 mm) and deep axial scan range (8 mm) permits the AS-OCT to cover the entire anterior chamber in one image frame.

Various AS OCT devices available commercially are Visante AS-OCT (Carl-Zeiss Meditech, Dublin, CA, USA), slit-lamp OCT (SL-OCT) (Heidelberg Engineering, Dossenheim, Germany), and Casia SS-1000 OCT (Tomey, Nagoya, Japan).

Visante optical coherence tomography (OCT; Carl Zeiss Meditec, Dublin, CA) and the slit-lamp

OCT (SL-OCT; Heidelberg Engineering GmbH, Dossenheim, Germany) are noncontact imaging devices that have been shown to be repeatable and reproducible for measurement of the angle. Both are time-domain OCT with a respective scan speed of 2000 A-scans and 200 A-scans/s. With a frame size of 256 A-scans and 215 A-scans, respectively, it takes 0.125 s for Visante OCT and 1.075 s for SL-OCT to capture a single cross-sectional image. The relatively slow scan rate limits the sampling density for both instruments and may increase the propensity for motion artifact for SL-OCT [12].

There has been an evolution in the Anterior segment OCT from time domain to spectral domain and to the newer swept source OCT. A potential limitation of the TD-OCT for detecting irido-corneal contact in closed angles is that detailed and consistent imaging of any structure other than the SS is poor. The diagnosis of a closed angle is thus based on identifying contact between the iris and the angle wall anterior to the SS, which is a more posteriorly located structure than the TM. Thus, the SS is used as a surrogate landmark instead of the trabecular meshwork (TM), as it is more easily visible on TD-OCT imaging.

The newer Fourier-imaging-based SD-OCT provides real-time imaging with a higher axial (5 μm) and transverse (15 μm) resolution and a scan rate that is 50–60 times faster (26,000 A scans/s) than time-domain OCT devices, which serves to limit motion artifact. The SD-OCT uses a super-luminescent diode laser with a wavelength of 840 nm. Due to the different wavelength of light used, faster acquisition rates, higher resolution, and a reduction in motion artifact, the SD-OCT allows more structures of the ACA to be visualized, like the trabecular meshwork (TM) and Schwalbe's line (SL). This is a distinct advantage over the earlier TD-OCT devices. There are many currently available devices like the Cirrus HD-OCT (Zeiss Meditec, Dublin, CA) and RTVue (Optovue, Fremont, CA, USA). By attaching the cornea-anterior module (CAM), the RTVue can take an image with dimensions of 6×2 mm (CAM-L) or 2×2 mm (CAM-S) at the angle; CAM-L provides lower magnification with a wider field. The Cirrus SD-OCT also allows anterior segment imaging with a built-in 60-diopter aspheric lens. The current software of both the SD-OCT devices does not take into consideration the effect of refraction at the air-cornea and cornea-aqueous interfaces (dewarping) [13].

The recent Casia SS-1000 OCT (Tomey, Nagoya, Japan) is a Fourier-domain device that uses a swept laser source at a wavelength of 1310 nm (that is same as the TD-OCT) and a scan speed of 30,000 A-scans/s. The device has a scanning range of 16 mm that allows an entire cross-section of the anterior chamber (128 cross-sections, each with 512 A-scans) to be captured simultaneously in 2.4 s. The SS-OCT can thus simultaneously obtain multiple radial scans of the entire circumference of the ACA. The SS-OCT also allows visualization of the SS, SL, and TM.

The majority of OCT machines (Fig. 56.2) have a motorized chin rest and an internal fixation target that can be adjusted according to the subject's distance refraction, permitting image acquisition without confounding results by accommodation (Fig. 56.2). The SL-OCT system, on the other hand, is incorporated onto a slit-lamp with the scanner unit permanently attached to the slit-lamp illumination. During image acquisition, the patient should place his chin and forehead against the headrest of the slit-lamp and focus on a point 2–3 m away. The examiner has to position the slit-lamp light beam onto the location to be scanned. The scanned images of these devices are processed by customized software.

The infrared light used by both AS-OCT systems cannot image the anterior segment through the eyelids. The eyelids must be gently moved away before obtaining scans of the superior and inferior ACA.

56.2.3 Scheimpflug Photography

The Pentacam (Oculus Optigerate GmbH) (Fig. 56.3) images the anterior segment of the eye by a rotating Scheimpflug camera measurement. It is being used extensively by cornea and refractive surgeons for determining intraocular lens (IOL) power, phakic IOL implantation, and for

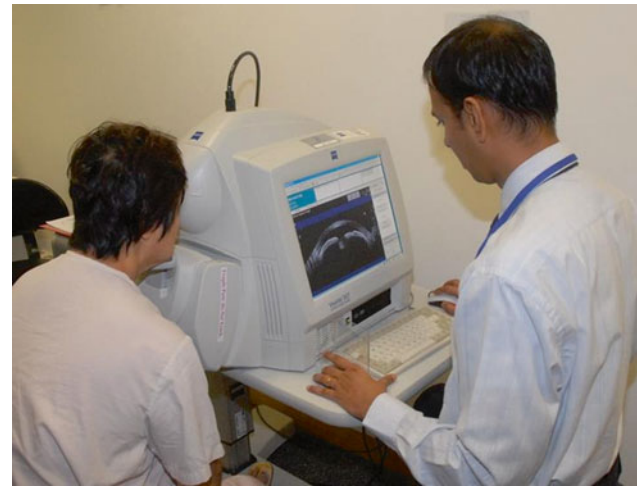

Fig. 56.2 Visante AS-OCT machine imaging the anterior chamber angle of patient who is seated for scan

Fig. 56.3 Pentacam Scheimpflug camera

determining corneal topography prior to refractive surgery. It is entirely noncontact and takes about 2 s to perform 12–50 single image captures; the device allows for small eye movements. In total, up to 25,000 true elevation points from the anterior and posterior corneal surfaces are measured that create a three-dimensional model of the anterior segment. The software measures the anterior chamber depth from the corneal endothelium to the anterior lens surface, mean and minimum ACA, and anterior chamber volume. The patient sits in front of the camera with his chin on a rest while the measurements are taken. The requirement of fixation makes measurements difficult in children, some older subjects, and in those with nystagmus [14]. The angle details are often difficult to make out due to light scattering; this means that the scleral spur cannot be identified and hence limits its use in angle closure.

Summary for the Clinician

- UBM uses high frequency ultrasound to image the ACA, but requires contact with the eye to do so.
- AS-OCT offers a noncontact, rapid method to image the angle.
- The Pentacam (Scheimpflug photography) images the anterior chamber, but is limited in its ability to assess the angle.

56.3 When Should UBM and AS-OCT Be Ordered: Is One Device Considered Better than the Other?

Both UBM and AS-OCT can be used to image the ACA. They each have their strengths and weaknesses for various clinical conditions, and unfortunately neither device is perfect for every patient. The AS-OCT can image the entire cross-section of the anterior chamber allowing visualization of two quadrants simultaneously. The AS-OCT is a noncontact device that allows the patient to be examined sitting down. Although the UBM is a noninvasive device, the eye needs to be kept open using a polymer or silicone cup since the probe moves in an immersion bath and imaging is routinely done with the patient in the supine position. Some skill is required for UBM operation and the process takes longer than AS-OCT. A newer generation of UBM devices is becoming available that incorporates the immersion bath within the probe, thereby allowing examination of a seated patient; however, these devices still require a coupling medium to be applied to the eye and for the eyelids to be separated manually.

In contrast to UBM, the infrared light used by AS-OCT is blocked by iris pigment, which precludes assessment of the structures located behind the iris. Furthermore, due to degradation of the light by sclera, the AS-OCT is not capable of fully imaging the ciliary body. Thus, for conditions such as plateau iris or malignant glaucoma, UBM is more useful. AS-OCT is helpful in determining angle morphology in patients who have an acute eye condition as it is noncontact and the UBM would cause discomfort and might be difficult to perform. Also, it might be the ideal imaging tool for children.

Radhakrishnan et al. compared the accuracy of classification of narrow ACAs using quantitative imaging by UBM and a prototype version of Visante AS-OCT [11]. Angle assessment was performed quantitatively by measuring several ACA parameters (angle opening distance, angle recess area, trabecular-iris space area (TISA), trabecular-iris contact length) using images obtained in the nasal and temporal quadrants. The authors observed that the two devices had similar discriminatory power to detect eyes with narrow angles. Both devices provided similar mean values for various ACA parameters, and when a statistically significant difference was present (angle recess area at 500 and 750 μ, TISA at 750 μ), UBM tended to give smaller measurements. A later study comparing the currently available commercial version of the AS-OCT and UBM showed that angle parameters obtained by both devices were also comparable [15].

Summary for the Clinician

- UBM and AS-OCT provide similar quantitative measurements for various angle parameters, although UBM may give smaller measurements for angle recess area and TISA
- The strength of UBM over AS-OCT is its ability to visualize the ciliary body and lens behind the iris
- The weaknesses of UBM compared to AS-OCT are the need for a skillful technician, longer image acquisition time, and imaging of only a part of the eye's cross-section
- The strengths of AS-OCT over UBM are its noncontact nature, shorter image acquisition time, simplicity of image acquisition, and ability to image entire cross-section of eye
- The weaknesses of AS-OCT over UBM are its inability to image behind the iris or through eyelids

56.4 How Should the Test Results Be Interpreted and Used to Help Treat the Patient?

With the UBM, image analysis of the ACA configuration and its interpretation is dependent on determining the location of the scleral spur (SS) [6]. The SS, a wedge-shaped structure that

denotes the posterior part of the ACA, is an anatomical landmark used to locate the trabecular meshwork (TM), which sits approximately 250–500 μm anterior to the SS along the angle wall. Another landmark, Schwalbe's line (SL), represents the termination of Descemet's membrane and is the anterior most structure of the ACA.

UBM and AS-OCT images can be analyzed quantitatively or qualitatively. For UBM, semi-automated software such as the UBMPro 2000 (Paradigm Medical Industries Inc.) is available [16]. All OCT devices have proprietary built-in software that can be used to quantify the images captured. There is custom-made image processing software available for the AS-OCT devices. One of them, the Zhongshan Angle Assessment Program (ZAAP, Guangzhou, China) software, automatically extracts the grey-scale image portion of the output file and performs noise and contrast conditioning. A binary copy of the image will then be produced, with pixels defined according to a calculated brightness/darkness threshold value. Algorithms then define the borders of the corneal epithelium and endothelium and the anterior surface of the iris [17].

56.4.1 Qualitative Analysis

Both UBM and the AS-OCT have been useful in confirming the presence of angle closure. Angle closure is denoted by contact between the iris and angle wall anterior to the scleral spur (Figs. 56.4 and 56.5). Moderate to good agreement has been shown between UBM and gonioscopy for the diagnosis of angle closure [18, 19]. The AS-OCT identifies closed angles more frequently than gonioscopy, especially in the vertical quadrants. Different rates of angle closure detection between the two examinations can be explained by variations in lighting conditions (AS-OCT can be performed in complete darkness while gonioscopy requires slit-lamp illumination), inadvertent opening of the angles during gonioscopy, the iris profile, and level of irido-angle contact [20, 21].

Various studies have described qualitative angle changes under different imaging conditions or after various interventions. For example, imaging under dark and light conditions provides information on illumination-induced angle configuration changes (Fig. 56.6) [8, 22]. Studies have reported changes in the angle after laser iridotomy, as well. Once pupillary block is relieved, the angle width increases accompanied with 'flattening' of the iris (Figs. 56.7 and 56.8) [23]. Similar results have been shown in angle closure eyes undergoing cataract surgery, although the samples in these studies are small [24, 25].

UBM has been useful in elucidating mechanisms of angle closure. Plateau iris, a non-pupillary block mechanism of angle closure, has been demonstrated both qualitatively and quantitatively using UBM (Fig. 56.9) [1, 26, 27]. Some cases of angle closure are caused by iris or ciliary body cysts, which cannot be seen with gonioscopy but are uncovered by UBM (Fig. 56.10) [28]. Pigment dispersion syndrome, an open angle disease, has also benefited from UBM,

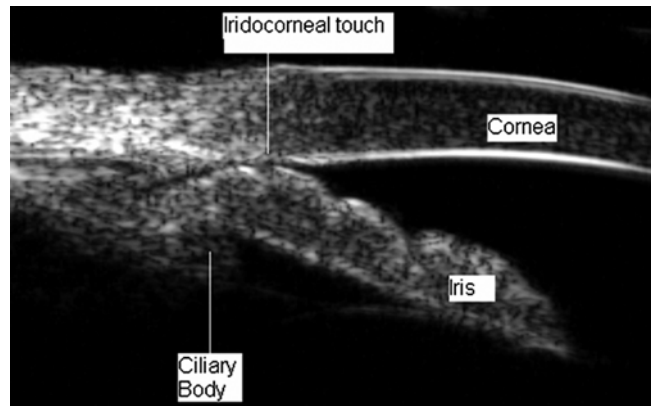

Fig. 56.4 UBM scan of a closed angle; there is irido-angle touch obstructing the trabecular meshwork

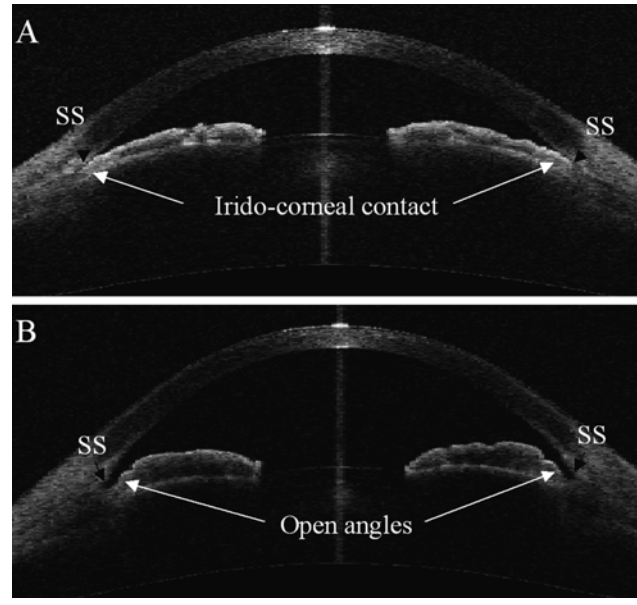

Fig. 56.5 AS-OCT images: (**a**) showing irido-angle contact in two quadrants of an eye and a shallow anterior chamber compared to an eye with open angles and deeper anterior chamber (**b**)

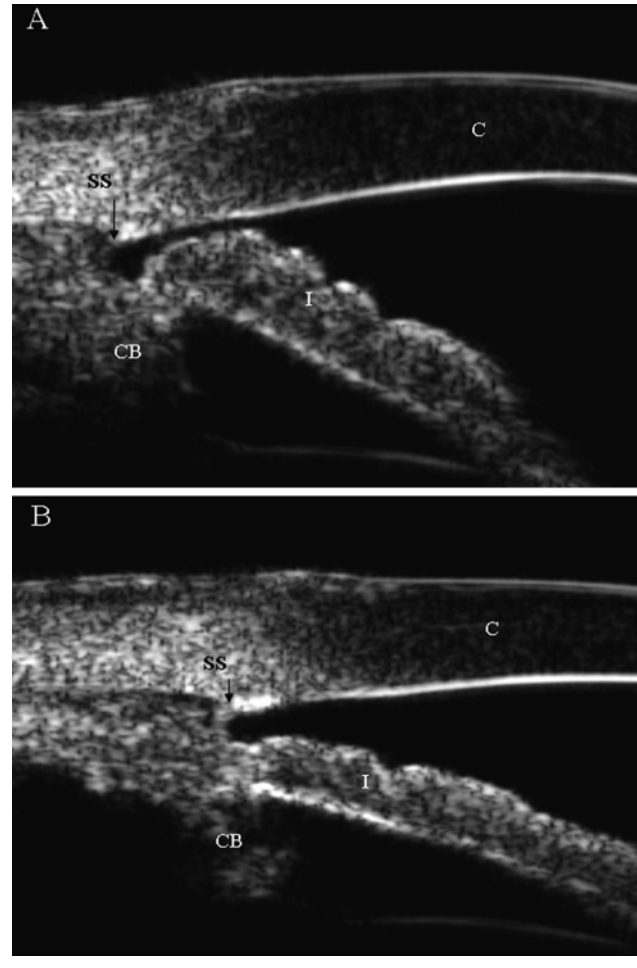

Fig. 56.6 UBM images showing changes in angle configuration and iris contour in dark (**a**) and light (**b**) conditions

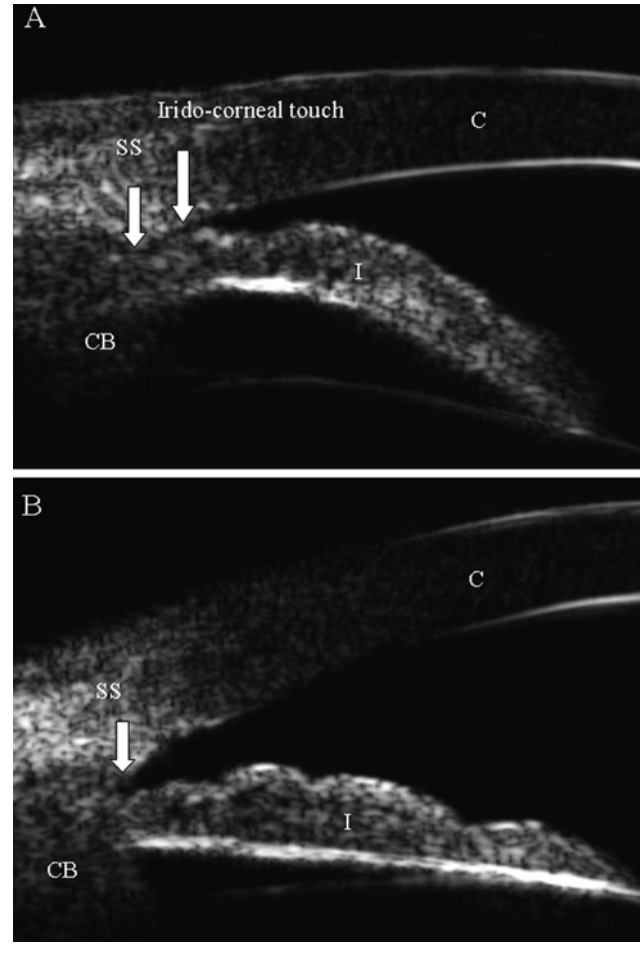

Fig. 56.7 UBM images showing the effect of laser iridotomy on the angle configuration in a quadrant of an eye with narrow angles; irido-corneal contact and iris convexity (**a**) appears to be relieved after laser iridotomy (**b**)

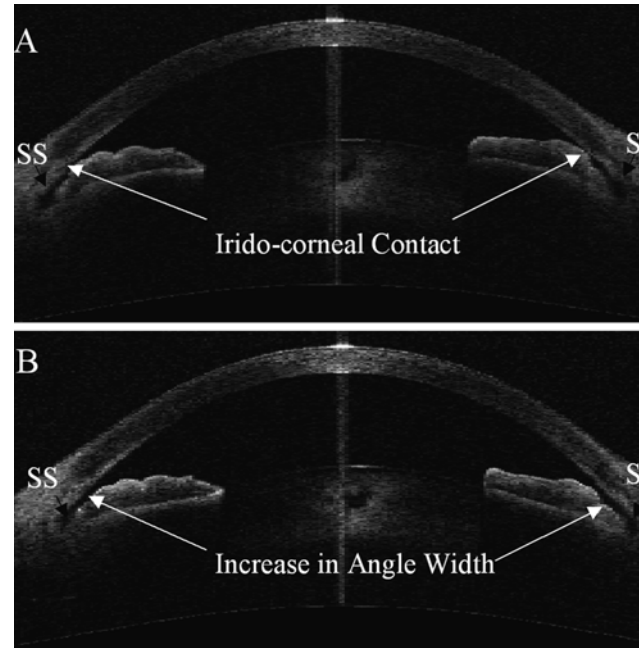

Fig. 56.8 AS-OCT images showing changes in anterior chamber configuration in an eye with narrow angles before (**a**) and after (**b**) laser iridotomy

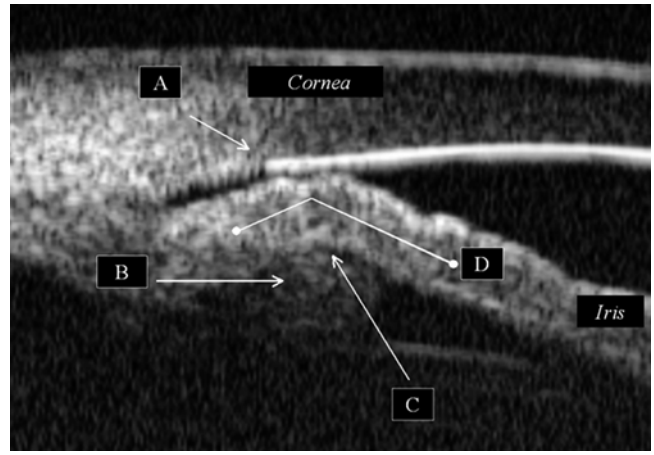

Fig. 56.9 UBM image in a quadrant showing plateau iris after laser peripheral iridotomy. Features shown: (**a**) irido-angle touch, (**b**) anteriorly rotated ciliary process, (**c**) absent ciliary sulcus, and (**d**) iris angulation

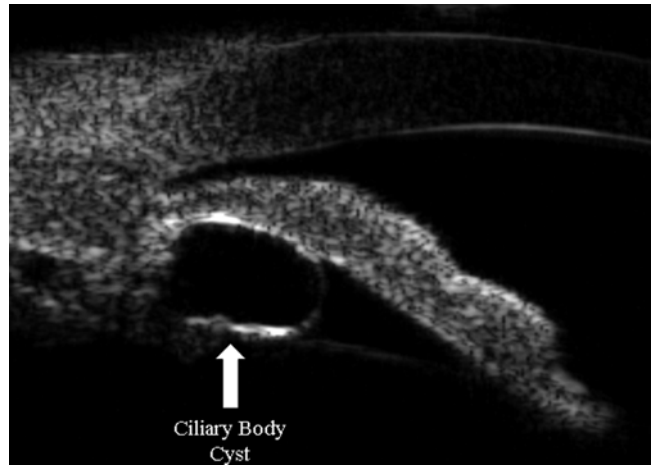

Fig. 56.10 UBM images showing a ciliary body cyst pushing up the peripheral iris

which can demonstrate the iris concavity that occurs due to 'reverse pupillary block' [29]. UBM has been used to document other conditions like cyclodialysis clefts and ciliochoroidal effusion (Figs. 56.11 and 56.12) [30]. Solid and cystic lesions of the iris and ciliary body may also be differentiated by UBM.

In OCT images, a'closed' ACA is defined as the presence of any contact between the iris and angle wall anterior to the SS, which is different from gonioscopic classification of appositional contact; the limitation has been the inability to visualize TM with TD-OCTs. This has been the reason for earlier reports of TD-OCT detecting more angles as closed compared to gonioscopy. OCT imaging can also help in understanding the mechanisms of angle closure. Change in the iris curvature post-iridotomy would signify that pupil block has been relieved. Further, an increase in angle width post iridotomy is another parameter that can be assessed. With the advent of the SD-OCT and the SS-OCT, we can identify newer landmarks and structures like the SL, TM, and the Schlemm's canal (SC), which allow us to define the boundaries of the ACA with better precision than with the earlier TD-OCT [13, 25].

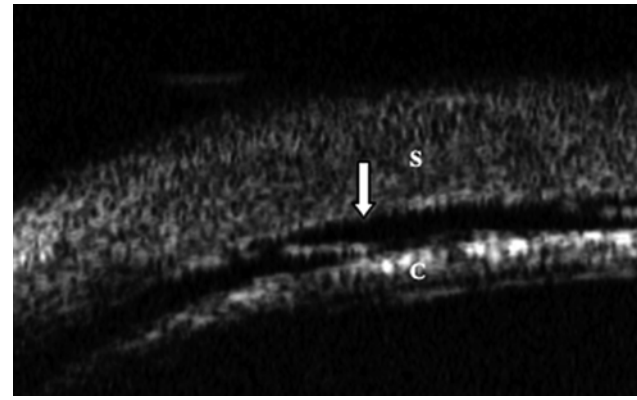

Fig. 56.11 UBM image showing ciliochoroidal effusion in an eye with acute angle closure; *S* sclera, *C* choroid

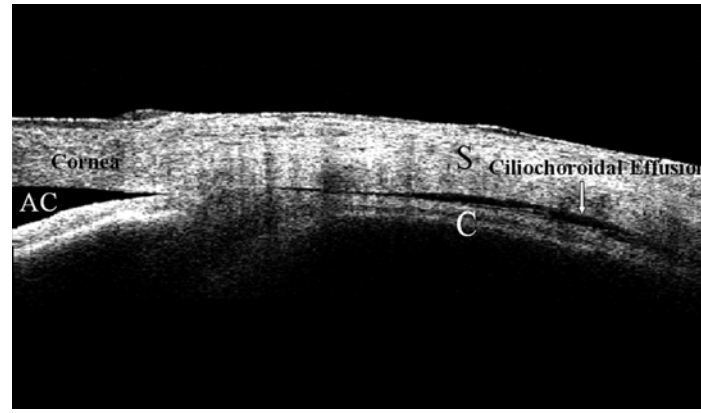

Fig. 56.12 AS-OCT scan showing ciliochoroidal effusion in an eye with acute angle closure; *S* sclera, *C* choroid, *AC* anterior chamber

56.4.2 Quantitative Analysis

The most commonly used parameters for quantitative analysis of the angle are as follows: (1) angle opening distance (**AOD**), which is the distance between the angle wall and iris along a line perpendicular to the trabecular meshwork and cornea at a specified distance (either at 250 or 500 μ) from the scleral spur, (2) the angle recess area (**ARA**), which is the area of space lying between the line taken for the AOD and the angle recess, and more recently, (3) the trabecular iris space area (**TISA**) for the AS-OCT specifically, which excludes the nonfunctioning area posterior to the scleral spur [16, 31, 32]. Figure 56.13 shows these parameters. Newer parameters for quantitative assessment of ACA using AS-OCT include (1) lens vault (**LV**), measured manually as the perpendicular distance between the anterior pole of the crystalline lens and the horizontal line joining the two scleral spurs and (2) anterior chamber width (**ACW**), which is the measurement of the spur to spur distance (Fig. 56.14).

Various iris parameters have been evaluated recently. Iris volume is estimated by capturing four cross-sectional images of the anterior segment at 45°-intervals (Fig. 56.15). Iris thickness (**IT750** and **IT2000**) is defined as thickness measured at 750 and 2000 μm from the scleral spur, respectively (Fig. 56.15). Iris curvature (**I-curv**) is measured by custom-made software where a line is drawn from the peripheral-most part to the central point of the iris pigment epithelium (**IPE**); then a perpendicular line is extended from this line to the IPE at the point of greatest convexity [33, 34] (Fig. 56.15). The **IArea**, another parameter, is calculated as the total cross-sectional area of the iris (from SS to pupil) (Fig. 56.15).

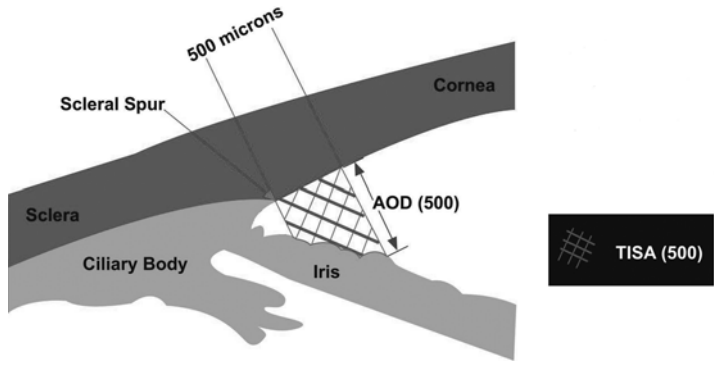

Fig. 56.13 Diagrammatic representation of parameters that are used for quantifying the anterior chamber angle: angle opening distance (AOD) at 500 μm from the scleral spur, angle recess area (ARA) at 500 μm, and trabecular-iris space area (TISA) at 500 μm. For TISA, the area behind the scleral spur is not included. Both ARA and TISA follow the iris contour

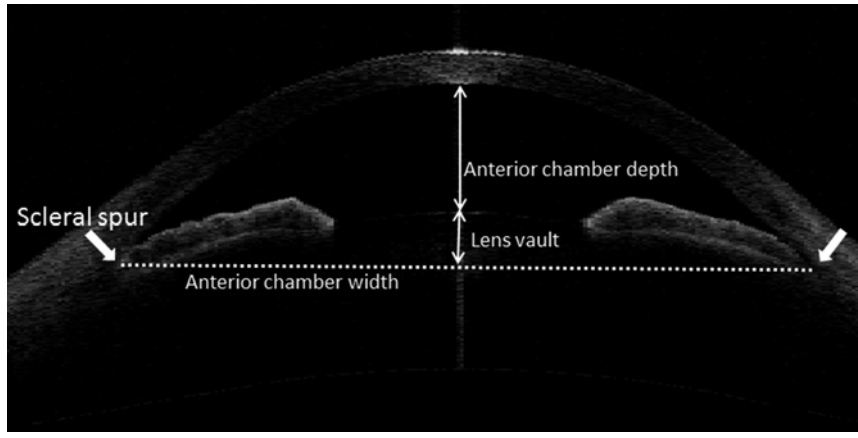

Fig. 56.14 AS-OCT image illustrating the measurement of lens vault. *Bold arrows* indicate the position of the scleral spur

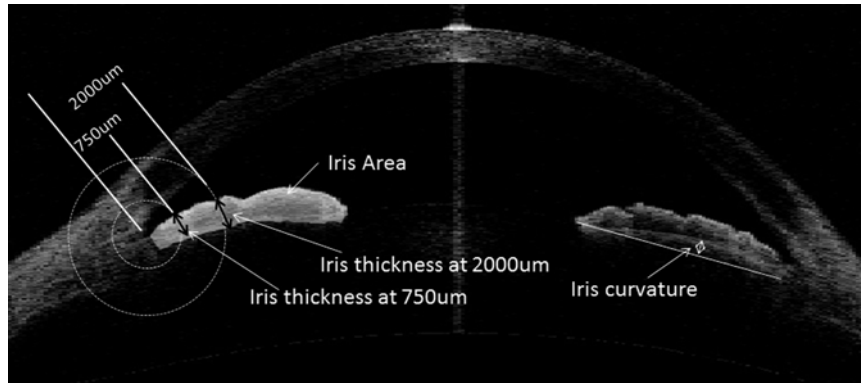

Fig. 56.15 AS-OCT image showing iris thickness measured at 750 and 2000 μm from the scleral spur (IT750 and IT2000), respectively, and Iris area (I-Area which is calculated as the cumulative cross-sectional area of the full length of the iris) and Iris curvature (I-Curv, calculated using software that draws a line from the most peripheral to the most central points of iris pigment epithelium, and then a perpendicular line extending from this line to the iris pigment epithelium at the point of greatest convexity)

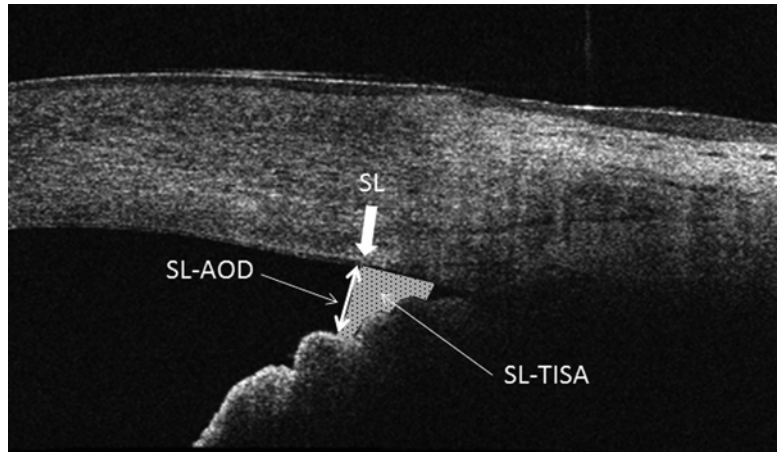

Fig. 56.16 SD-OCT image showing Schwalbe's line-angle opening distance (SL-AOD) and Schwalbe's line-trabecular-iris space area (SL-TISA)

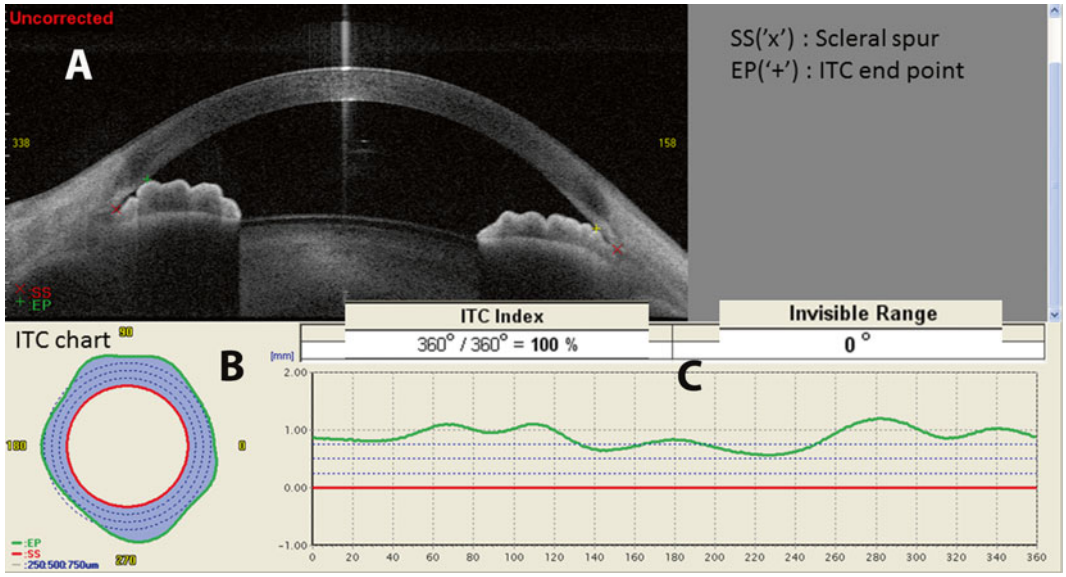

Fig. 56.17 The iris-trabecular contact (ITC) index analysis for a closed angle using SS-OCT. (**a**) Single frame of the cross-section of the anterior chamber. The colored "x" represents the scleral spur (SS) markings, and the "+" represents the ITC end point (EP); both points are marked by the observer grading the image. (**b**) The ITC chart with the *blue area* represents the amount and distribution of ITC. (**c**) The ITC graph with the *Y* axis represents ITC (in arbitrary units), and the *X* axis represents the degree of the angle. The *green graph* above the *red line* (representing SS) denotes the amount of angle-closure (measured as the ITC index)

Two parameters based on the SL as an anatomical landmark are **SL-AOD** and **SL-TISA**, to quantify angle width; these have been shown to have a high reproducibility and a good correlation with conventional SS parameters and gonioscopic classification [35] (Fig. 56.16). The irido-trabecular contact (**ITC**) index is a new parameter available on the SS-OCT that gives a measure of the extent of the irido-trabecular contact over 360° of the ACA; it has been shown to have moderate agreement with gonioscopy [33] (Fig. 56.17).

Radhakrishnan et al. found that the short-term intra- and inter-observer reproducibility and long-term intra-observer reproducibility varied from good to excellent in the nasal and temporal quadrants, and from poor to good in the inferior quadrant using a prototype version of Visante OCT [36].

Recent studies have reported good intra-observer reproducibility using proprietary software, but fair inter-observer reproducibility for these angle parameters; the subjective marking of the SS is a potential limiting determinant [17, 37, 38].

Summary for the Clinician

- The scleral spur is an important landmark that needs to be detected for quantitative angle analysis on both UBM and the earlier TD-OCT. Schwalbe's line might serve as an alternative landmark with the newer SD- and SS-OCT devices.
- Both UBM and AS-OCT have moderate-to-good agreement with gonioscopy. The AS-OCT tends to detect more closed angles than gonioscopy when angle images are qualitatively assessed for angle closure.

References

1. Foster PJ, Devereux JG, Alsbirk PH, et al. Detection of gonioscopically occludable angles and primary angle closure glaucoma by estimation of limbal chamber depth in Asians: modified grading scheme. Br J Ophthalmol. 2000;84:186–92.
2. Nolan WP, Foster PJ, Devereux JG, et al. YAG laser iridotomy treatment for primary angle closure in east Asian eyes. Br J Ophthalmol. 2000;84:1255–9.
3. Liebmann JM, Ritch R. Ultrasound biomicroscopy of the anterior segment. J Am Optom Assoc. 1996;67:469–79.
4. Pavlin CJ, Harasiewicz K, Sherar MD, et al. Clinical use of ultrasound biomicroscopy. Ophthalmology. 1991;98:287–95.
5. Radhakrishnan S, Rollins AM, Roth JE, et al. Real-time optical coherence tomography of the anterior segment at 1310 nm. Arch Ophthalmol. 2001;119:1179–85.
6. Pavlin CJ, Foster FS. Ultrasound biomicroscopy of the eye. New York: Springer; 1995.
7. Sakata LM, Lavanya R, Friedman DS, et al. Assessment of the scleral spur in anterior segment optical coherence tomography images. Arch Ophthalmol. 2008;126:181–5.
8. Pavlin CJ, Foster FS. Plateau iris syndrome: changes in angle opening associated with dark, light, and pilocarpine administration. Am J Ophthalmol. 1999;128:288–91.
9. Goldsmith JA, Li Y, Chalita MR, et al. Anterior chamber width measurement by high speed optical coherence tomography. Ophthalmology. 2005;112:238–44.
10. Hoerauf H, Gordes RS, Scholz C, et al. First experimental and clinical results with transscleral optical coherence tomography. Ophthalmic Surg Lasers. 2000;31:218–22.
11. Radhakrishnan S, Goldsmith J, Huang D, et al. Comparison of optical coherenc tomography and ultrasound biomicroscopy for detection of narrow anterior chamber angles. Arch Ophthalmol. 2005;123:1053–9.
12. Liu S, Yu M, Cong Y, Lam DS, et al. Anterior chamber angle imaging with swept-source optical coherence tomography: an investigation on variability of angle measurement. Invest Ophthalmol Vis Sci. 2011;52:8598–603.
13. Leung CK, Weinreb RN. Anterior chamber angle imaging with optical coherence tomography. Eye. 2011;25:261–7.
14. Rabsilber TM, Khoramnia R, Auffarth GU. Anterior chamber measurements using Pentacam rotating Scheimpflug camera. J Cataract Refract Surg. 2006;32:456–9.
15. Dada T, Sihota R, Gadia R, et al. Comparison of anterior segment optical coherence tomography and ultrasound biomicroscopy for assessment of the anterior segment. J Cataract Refract Surg. 2007;33:837–40.
16. Ishikawa H, Liebmann JM, Ritch R. Quantitative assessment of the anterior segment using ultrasound biomicroscopy. Curr Opin Ophthalmol. 2000;11:133–9.
17. Console JW, Sakata LM, Aung T, et al. Quantitative analysis of anterior segment optical coherence tomography images: the Zhongshan Angle Assessment Program. Br J Ophthalmol. 2008;92:1612–6.
18. Kaushik S, Jain R, Pandav SS, et al. Evaluation of the anterior chamber angle in Asian Indian eyes by ultrasound biomicroscopy and gonioscopy. Indian J Ophthalmol. 2006;54:159–63.
19. Narayanaswamy A, Vijaya L, Shantha B, et al. Anterior chamber angle assessment using gonioscopy and ultrasound biomicroscopy. Jpn J Ophthalmol. 2004;48:44–9.
20. Nolan WP, See JL, Chew PT, et al. Detection of primary angle closure using anterior segment optical coherence tomography in Asian eyes. Ophthalmology. 2007;114:33–9.
21. Sakata LM, Lavanya R, Friedman DS, et al. Comparison of gonioscopy and anterior segment ocular coherence tomography in detecting angle closure in different quadrants of the anterior chamber angle. Ophthalmology. 2008;115(5):769–74.
22. Woo EK, Pavlin CJ, Slomovic A, et al. Ultrasound biomicroscopic quantitative analysis of light-dark changes associated with pupillary block. Am J Ophthalmol. 1999;127:43–7.

23. Gazzard G, Friedman DS, Devereux JG, et al. A prospective ultrasound biomicroscopy evaluation of changes in anterior segment morphology after laser iridotomy in Asian eyes. Ophthalmology. 2003;110:630–8.
24. Nonaka A, Kondo T, Kikuchi M, et al. Angle widening and alteration of ciliary process configuration after cataract surgery for primary angle closure. Ophthalmology. 2006;113:437–41.
25. Pereira FA, Cronemberger S. Ultrasound biomicroscopic study of anterior segment changes after phacoemulsification and foldable intraocular lens implantation. Ophthalmology. 2003;110:1799–806.
26. Pavlin CJ, Ritch R, Foster FS. Ultrasound biomicroscopy in plateau iris syndrome. Am J Ophthalmol. 1992;113:390–5.
27. Kumar RS, Baskaran M, Chew PTK, et al. Prevalence of plateau iris in primary angle closure suspects: an ultrasound biomicroscopy study. Ophthalmology. 2008;115:430–4.
28. Fine N, Pavlin CJ. Primary cysts in the iridociliary sulcus: ultrasound biomicroscopic features of 210 cases. Can J Ophthalmol. 1999;34:325–9.
29. Potash SD, Tello C, Liebmann J, et al. Ultrasound biomicroscopy in pigment dispersion syndrome. Ophthalmology. 1994;101:332–9.
30. Sakai H, Morine-Shinjyo S, Shinzato M, et al. Uveal effusion in primary angle-closure glaucoma. Ophthalmology. 2005;112:413–9.
31. Pavlin CJ, Harasiewicz K, Foster FS. Ultrasound biomicroscopy of anterior segment structures in normal and glaucomatous eyes. Am J Ophthalmol. 1992;113:381–9.
32. Radhakrishnan S, Huang D, Smith SD. Optical coherence tomography imaging of the anterior chamber angle. Ophthalmol Clin North Am. 2005;18:375–81.
33. Baskaran M, Ho SW, Tun TA, et al. Assessment of circumferential angle-closure by the iris-trabecular contact index with swept-source optical coherence tomography. Ophthalmology. 2013;120(11):2226–31. 1–6.
34. Nongpiur ME, Haaland BA, Friedman DS, et al. Classification algorithms based on anterior segment optical coherence tomography measurements for detection of angle closure. Ophthalmology. 2013;120:48–54.
35. Cheung CY, Zheng C, Ho CL, Kumar RS, et al. Novel anterior-chamber angle measurements by high-definition optical coherence tomography using the Schwalbe line as the landmark. Br J Ophthalmol. 2011;95:955–9.
36. Radhakrishnan S, See JL, Smith SD, et al. Reproducibility of angle chamber angle measurement obtained with anterior segment optical coherence tomography. Invest Ophthalmol Vis Sci. 2007;48:3683–8.
37. Tello C, Liebmann J, Potash SD, et al. Measurement of ultrasound biomicroscopy images: intraobserver and interobserver reliability. Invest Ophthalmol Vis Sci. 1994;35:3549–52.
38. Urbak SF, Pedersen JK, Thorsen TT. Ultrasound biomicroscopy. II. Intraobserver and interobserver reproducibility of measurements. Acta Ophthalmol Scand. 1998;76:546–9.

Angle-Closure Glaucoma: Medical Therapy

57

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Core Messages

- Medical therapy may be used alone for angle-closure glaucoma, but is usually used in conjunction with laser or surgical therapy.
- Medications used to treat acute angle-closure are generally the same as those used for open-angle glaucoma, but some differences do exist.
- Care must be taken when using pilocarpine and other miotics because of paradoxical effects this class of drug can have on angle-closure.

57.1 During an Acute Angle-Closure Attack, What Medications Are Indicated?

In an acute angle-closure (AAC) attack, the goal of treatment is to reduce intraocular pressure (IOP) and prevent progression to chronic angle-closure glaucoma and visual loss. Medication alone may break the AAC attack, but the primary role of medical therapy is to optimize conditions so that definitive treatment (laser iridotomy and/or cataract extraction) can be performed. Most classes of glaucoma medications may be utilized in the treatment of AAC glaucoma.

57.1.1 Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors (CAIs) reduce IOP by suppressing aqueous humor formation, presumably by inhibiting carbonic anhydrase in the ciliary epithelium [1–4]. CAIs are particularly suitable for treatment of AAC due to their rapid onset of action and their efficacy virtually under all ocular conditions. Oral CAIs, in the form of acetazolamide, reach peak plasma levels within 1 h and peak IOP reduction is achieved within 2 h [5]. Regular acetazolamide should be used instead of slow-release formulations (Diamox Sequels) in cases of AAC. Topical CAIs (dorzolamide, brinzolamide) also have peak IOP-lowering efficacy within 2 h post-administration. CAIs appear to have good IOP-lowering effect throughout the 24-h period [1, 3, 4, 6].

57.1.2 Beta-Blockers

Beta-blockers reduce IOP by decreasing the rate of aqueous humor formation and are also appropriate for AAC treatment [1, 3, 4, 7]. They have a

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rapid onset of action with initial effects occurring within 10–20 min and peak IOP reduction occurring approximately 2–3 h after administration [8, 9]. The question of whether or not to use beta-blockers during the nocturnal period is interesting, since there appears to be little or no IOP-lowering effect at night [6, 10]. However, if additional IOP-lowering is required, there is little harm in using topical beta-blockers, as long as no contraindications are present. Major contraindications include bronchospasm, congestive heart failure, bradycardia, and systemic hypotension.

57.1.3 Alpha-Agonists

Alpha-agonists also have a rapid onset of action, with peak IOP-lowering effect at around 2 h [11, 12]. Alpha-agonists commonly available for treatment of glaucoma include apraclonidine and brimonidine. Both are selective alpha-2-agonists that reduce IOP by inhibiting aqueous humor formation without affecting outflow facility [7, 13, 14], and possibly by increasing uveoscleral outflow [15]. Both appear to have additive effects with other aqueous suppressants and are suitable for treatment of AAC [16].

57.1.4 Prostaglandin Analogs

Prostaglandin analogs are potent IOP-lowering medications that work primarily by increasing uveoscleral outflow and conventional outflow facility [17–20]. Although they do appear to be effective in the treatment of chronic angle-closure glaucoma [21–26], their mechanism of action and delayed onset make them unsuitable for treatment of AAC glaucoma.

57.1.5 Hyperosmotic Agents

Hyperosmotic agents are given orally or intravenously. The mechanism of action of hyperosmotics is a transient increase in serum osmolality that draws water from the retinal and uveal vasculature [27]. Common oral medications include glycerol and isosorbide, while mannitol is given intravenously. These medications are useful for rapid, temporary reduction of IOP when other medications are inadequate. They are primarily used as temporizing measures in preparation for more definitive treatments including laser and incisional surgery.

57.1.6 Miotics

Miotics include direct- and indirect-acting cholinergic medications. Topical direct-acting cholinergics include pilocarpine and carbochol, while the most common indirect-acting cholinergic is echothiophate iodide. Miotics must be used with caution in cases of AAC since paradoxical reactions can occur with worsening of the condition (see Sect. 57.2). In particular, carbochol and echothiophate iodide should be avoided as they cause intense stimulation of the ciliary muscle with anterior movement of the lens–iris diaphragm [28]. Pilocarpine may be used cautiously after appropriate assessment is performed, as discussed later.

Summary for the Clinician

- Medical treatment of acute angle-closure glaucoma is a prelude to more definitive laser or surgical therapy.
- Most topical medications used for chronic open and closed-angle glaucoma are suitable for use with angle-closure glaucoma.
- Care must be taken with pilocarpine; other miotics are contraindicated.
- Prostaglandin analogs may be safely used, but likely provide little benefit in acute angle-closure.

57.2 Should Pilocarpine Be Avoided in Angle-Closure Patients?

Pilocarpine is a direct-acting cholinergic agonist that acts at the parasympathetic muscarinic receptors located in smooth muscle. It is available in

concentrations from 0.25 % to 10 %. It has a rapid onset of action, with initial IOP-lowering effect occurring within minutes and lasting 4–8 h [29].

Pilocarpine has multiple effects on the physiology of the eye. First, stimulation of parasympathetic nerves causes constriction of the pupillary sphincter resulting in miosis. This can be useful in cases of primary angle-closure glaucoma by pulling the iris root away from the trabecular meshwork, relieving the angle-closure. Second, pilocarpine induces constriction of the ciliary muscle, which has attachments to the scleral spur. Posterior displacement of the scleral spur with ciliary muscle contraction causes traction on the trabecular meshwork resulting in increased aqueous outflow facility [30, 31]. A third effect of pilocarpine results from the effect of ciliary muscle contraction on the lens. Relaxation of the zonules with ciliary muscle contraction causes a change in lens diameter and radius of curvature, resulting in accommodative myopia [28].

While the effects of pilocarpine are generally beneficial in both open- and closed-angle glaucoma, controversy over the use of pilocarpine in angle-closure patients exists due to possible counter-productive effects [32]. Increase in the anterior–posterior lens diameter with ciliary muscle contraction can reduce the anterior chamber depth [33]. Increased zonule laxity can result in anterior displacement of the lens, further shallowing the anterior chamber [34]. These effects can exacerbate existing angle-closure or trigger angle-closure in susceptible individuals. However, ultrasound biomicroscopic studies suggest that this effect is more pronounced in eyes with deeper anterior chambers, while eyes with shallower chambers have increased angle width after pilocarpine administration [35]. A further paradoxical effect may result from pupillary sphincter constriction, which may increase iris tone, lens–iris touch, and predispose to pupil block, although little direct evidence of this effect exists [36].

Because of the complex effects of pilocarpine, care should be taken when using it in angle-closure glaucoma patients. One should use the lower concentrations (0.5 % and 1 %) and avoid the higher concentrations, which will have a greater effect on the lens–iris diaphragm. Numerous cases of paradoxical reactions to miotics resulting in triggering or worsening of angle-closure have been reported in the literature [37–41] usually associated with secondary causes. Therefore, it is critical to differentiate primary angle-closure due to pupil block from secondary mechanisms including plateau iris, lens-induced glaucoma, or aqueous misdirection. These can usually be distinguished from pupil block by history and careful examination of the affected and contralateral eye. If lens-induced glaucoma, such as phacomorphic glaucoma and angle-closure secondary to spherophakia, aqueous misdirection, or angle-closure due to supraciliary choroidal effusion, is suspected, then pilocarpine and other miotics should be avoided. However, for most primary angle-closure patients, it can be a useful treatment once secondary angle-closure mechanisms have been ruled out and the IOP has been lowered sufficiently by other means to eliminate pupillary sphincter ischemia in AAC. In terms of the fellow eye of an AAC eye, many specialists avoid using pilocarpine except immediately prior to prophylactic laser iridotomy.

Summary for the Clinician

- Pilocarpine has multiple physiologic effects on the eye.
- Paradoxical reactions due to miotics, such as an increase in anterior–posterior lens diameter and anterior chamber shallowing, can result in worsening of angle-closure.
- Careful history and examination must be performed in angle-closure patients to differentiate primary angle-closure (pupil block) from secondary angle-closure mechanisms—miotics should not be used in many cases of secondary angle-closure.
- If used, low concentrations of pilocarpine are preferred.

References

1. Dailey RA, Brubaker RF, Bourne WM. The effects of timolol maleate and acetazolamide on the rate of aqueous formation in normal human subjects. Am J Ophthalmol. 1982;1993:232–7.
2. Ingram CJ, Brubaker RF. Effect of brinzolamide and dorzolamide on aqueous humor flow in human eyes. Am J Ophthalmol. 1999;128:292–6.
3. McCannel CA, Heinrich SR, Brubaker RF. Acetazolamide but not timolol lowers aqueous humor flow in sleeping humans. Graefes Arch Clin Exp Ophthalmol. 1992;230:518–20.
4. Topper JE, Brubaker RF. Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep. Invest Ophthalmol Vis Sci. 1985;26:1315–9.
5. Friedland BR, Mallonee J, Anderson DR. Short-term dose response characteristics of acetazolamide in man. Arch Ophthalmol. 1977;95:1809–12.
6. Orzalesi N, Rossetti L, Invernizzi T, Bottoli A, Autelitano A. Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. Invest Ophthalmol Vis Sci. 2000;41:2566–73.
7. Larsson LI. Aqueous humor flow in normal human eyes treated with brimonidine and timolol, alone and in combination. Arch Ophthalmol. 2001;119:492–5.
8. Zimmerman TJ, Kaufman HE. Timolol, dose response and duration of action. Arch Ophthalmol. 1997;95:605–7.
9. Zimmerman TJ, Kaufman HE. Timolol. A beta-adrenergic blocking agent for the treatment of glaucoma. Arch Ophthalmol. 1977;95:601–4.
10. Liu JH, Kripke DF, Weinreb RN. Comparison of the nocturnal effects of once-daily timolol and latanoprost on intraocular pressure. Am J Ophthalmol. 2004;138:389–95.
11. Gabelt BT, Robinson JC, Hubbard WC, et al. Apraclonidine and brimonidine effects on anterior ocular and cardiovascular physiology in normal and sympathectomized monkeys. Exp Eye Res. 1994;59:633–44.
12. Adkins JC, Balfour JA. Brimonidine. A review of its pharmacological properties and clinical potential in the management of open-angle glaucoma and ocular hypertension. Drugs Aging. 1998;12:225–41.
13. Schadlu R, Maus TL, Nau CB, Brubaker RF. Comparison of the efficacy of apraclonidine and brimonidine as aqueous suppressants in humans. Arch Ophthalmol. 1998;116:1441–4.
14. Gharagozloo NZ, Relf SJ, Brubaker RF. Aqueous flow is reduced by the alpha-adrenergic agonist, apraclonidine hydrochloride (ALO 2145). Ophthalmology. 1988;95:1217–20.
15. Toris CB, Gleason ML, Camras CB, Yablonski ME. Effects of brimonidine on aqueous humor dynamics in human eyes. Arch Ophthalmol. 1995;113:1514–7.
16. Maus TL, Nau C, Brubaker RF. Comparison of the early effects of brimonidine and apraclonidine as topical ocular hypotensive agents. Arch Ophthalmol. 1999;117:586–91.
17. Brubaker RF. Mechanism of action of bimatoprost (lumigan). Surv Ophthalmol. 2001;45 Suppl 4:S347–51.
18. Toris CB, Camras CB, Yablonski ME. Effects of phxa41, a new prostaglandin f2 alpha analog, on aqueous humor dynamics in human eyes. Ophthalmology. 1993;100:1297–304.
19. Toris CB, Zhan G, Camras CB. Increase in outflow facility with unoprostone treatment in ocular hypertensive patients. Arch Ophthalmol. 2004;122:1782–7.
20. Toris CB, Zhan G, Fan S, et al. Effects of travoprost on aqueous humor dynamics in patients with elevated intraocular pressure. J Glaucoma. 2007;16:189–95.
21. Aung T, Chan YH, Chew PT. Degree of angle-closure and the intraocular pressure-lowering effect of latanoprost in subjects with chronic angle-closure glaucoma. Ophthalmology. 2005;112:267–71.
22. Chen MJ, Chen YC, Chou CK, Hsu WM. Comparison of the effects of latanoprost and travoprost on intraocular pressure in chronic angle-closure glaucoma. J Ocul Pharmacol Ther. 2006;22:449–54.
23. Chen MJ, Chen YC, Chou CK, Hsu WM. Comparison of the effects of latanoprost and bimatoprost on intraocular pressure in chronic angle-closure glaucoma. J Ocul Pharmacol Ther. 2007;23:559–66.
24. Chew PT, Aung T, Aquino MV, Rojanapongpun P. Intraocular pressure-reducing effects and safety of latanoprost versus timolol in patients with chronic angle-closure glaucoma. Ophthalmology. 2004;111:427–34.
25. Kook MS, Cho HS, Yang SJ, Kim S, Chung J. Efficacy of latanoprost in patients with chronic angle-closure glaucoma and no visible ciliary-body face: a preliminary study. J Ocul Pharmacol Ther. 2005;21:75–84.
26. Sakai H, Shinjyo S, Nakamura Y, et al. Comparison of latanoprost monotherapy and combined therapy of 0.5% timolol and 1% dorzolamide in chronic primary angle-closure glaucoma (CACG) in Japanese patients. J Ocul Pharmacol Ther. 2005;21:483–9.
27. Feitl ME, Krupin T. Hyperosmotic agents. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas, vol. 3. 2nd ed. St. Louis: Mosby-Year Book; 1996. p. 1483–8.
28. Nardin GF, Zimmerman TJ. Ocular cholinergic agents. In: Ritch R, Shields MB, Krupin T, editors. The glaucomas, vol. 3. 2nd ed. St. Louis: Mosby-Year Book; 1996. p. 1399–407.
29. Taylor P. Cholinergic agonist. In: Gilman AG, Goodman LS, Rall TW, Murad F, editors. The pharmacological basis of therapeutics. 7th ed. New York: Macmillan; 1985. p. 100–9.
30. Kaufman PL, Barany EH. Loss of acute pilocarpine effect on outflow facility following surgical disinsertion and retrodisplacement of the ciliary muscle from the scleral spur in the cynomolgus monkey. Invest Ophthalmol. 1976;15:793–807.
31. Lutjen-Drecoll E, Wiendl H, Kaufman PL. Acute and chronic structural effects of pilocarpine on monkey

outflow tissues. Trans Am Ophthalmol Soc. 1998;96:171–91; discussion 192–175.
32. Ritch R. The pilocarpine paradox. J Glaucoma. 1996;5:225–7.
33. Francois J, Goes F. Ultrasonographic study of the effect of different miotics on the eye components. Ophthalmologica. 1977;175:328–38.
34. Wilkie J, Drance SM, Schulzer M. The effects of miotics on anterior-chamber depth. Am J Ophthalmol. 1969;68:78–83.
35. Kobayashi H, Kobayashi K, Kiryu J, Kondo T. Ultrasound biomicroscopic analysis of the effect of pilocarpine on the anterior chamber angle. Graefes Arch Clin Experimen Ophthalmol. 1997;235: 425–30.
36. Quigley HA, Friedman DS, Congdon NG. Possible mechanisms of primary angle-closure and malignant glaucoma. J Glaucoma. 2003;12:167–80.
37. Gorin G. Angle-closure glaucoma induced by miotics. Am J Ophthalmol. 1966;62:1063–7.
38. Merritt JC. Malignant glaucoma induced by miotics postoperatively in open-angle glaucoma. Arch Ophthalmol. 1977;95:1988–9.
39. Rieser JC, Schwartz B. Miotic-induced malignant glaucoma. Arch Ophthalmol. 1972;87:706–12.
40. Pecora JL. Malignant glaucoma worsened by miotics in a postoperative angle-closure glaucoma patient. Ann Ophthalmol. 1979;11:1412–4.
41. Mapstone R. Acute shallowing of the anterior chamber. Br J Ophthalmol. 1981;65:446–51.

Angle-Closure Glaucoma: Surgical Management of Acute Angle-Closure Glaucoma

58

Jian Ge and Xiulan Zhang

Core Messages

- Anterior chamber paracentesis and cataract extraction are alternative options in the management of acute angle-closure attacks.
- Anterior chamber paracentesis does not relieve pupillary block.
- There are unique risks and complications to performing anterior chamber paracentesis and phacoemulsification in the setting of acute angle-closure.
- Phacomorphic glaucoma is a unique type of pupillary block glaucoma.
- In the setting of an occludable angle and cataract, whether to perform an iridotomy first or to proceed directly to cataract extraction is currently debated.

58.1 What Is the Role of Paracentesis in the Management of Acute Angle-Closure Glaucoma? Technically, How Should This Be Performed if the Anterior Chamber Is Very Shallow?

The initial treatment for acute primary angle-closure aims to reduce the intraocular pressure (IOP) as rapidly as possible to relieve symptoms and prevent further ocular tissue damage. Traditionally, IOP is lowered by topical or systemic hypotensive medications, which often will break the acute attack, and then the pupillary block is relieved by laser peripheral iridotomy (LPI). A number of groups across the world have described other procedures to break an attack of acute angle-closure, including argon laser peripheral iridoplasty, immediate anterior chamber paracentesis, and early cataract or lens extraction by phacoemulsification [1–12]. While these procedures can work to break an attack, they have not been widely adopted due to potential complications and the fact that they may not resolve the problem of pupillary block (except in the case of cataract extraction).

Immediate paracentesis has been shown to be both safe and effective in reducing IOP and eliminating the symptoms of acute angle-closure [1, 2, 5–8]. The instruments for immediate paracentesis are readily available in most eye clinics and even in some emergency rooms. They include a sterile eye prep, topical antibiotics, a speculum, slit lamp or operating microscope, and a sharp

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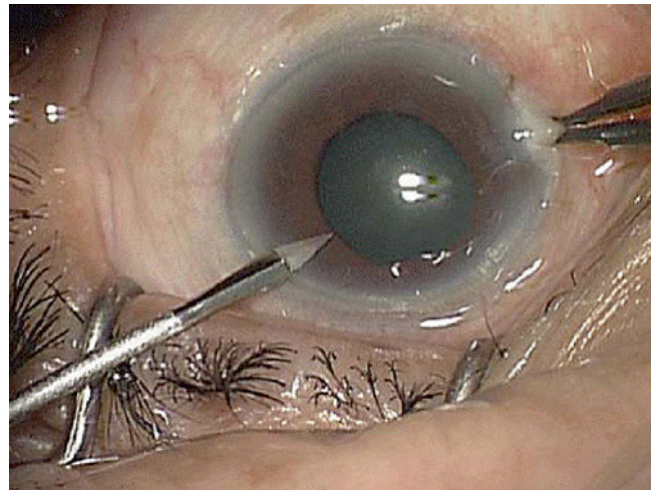

Fig. 58.1 Immediate anterior chamber paracentesis is performed in a very shallow anterior chamber by using the V-Lance™ knife (20 Gauge, 1.3 mm, Alcon). The procedure is performed with the patient lying supine under the microscope

blade or needle. We use either the V-Lance™ knife (20 Gauge, 1.3 mm, Alcon) (Fig. 58.1) or a capsulotomy needle. The patient can either lie supine under a microscope or sit at a slit lamp [1, 5, 6, 13–15]. The paracentesis only takes a few seconds to perform. It is best to shrink the vitreous volume with intravenous mannitol, which is given before the procedure [5].

When the anterior chamber is deep, a paracentesis is very easily performed [5, 6]. However, when the chamber is very shallow, technical difficulties can arise. Paracentesis can make the anterior chamber even shallower leading to complications, such as iris prolapse and endophthalmitis, corneal decompensation, or malignant glaucoma.

It is important to note that a paracentesis does not eliminate pupillary block. After a successful paracentesis, the pressure may rise again causing pain and ischemia due to unresolved pupillary block. Laser iridotomy remains the definitive treatment in these patients. Medical therapy for the pressure is generally initiated simultaneously with preparation for the paracentesis.

There are many potential risks with performing paracentesis in the setting of acute angle-closure. These complications include damage to the cornea, iris, or lens; infection; choroidal hemorrhage; decompression retinopathy; hyphema; and malignant glaucoma. Endophthalmitis has been reported after paracentesis, therefore aseptic techniques are mandatory [6, 14, 16].

The benefit of anterior chamber paracentesis is that it can very quickly lower IOP and relieve symptoms of acute angle-closure when there is no laser available for iridotomy. However, this procedure does not relieve the pupillary block that causes acute angle-closure and it does have significant potential complications. Prospective randomized clinical trials are needed to see if there is a role for and long-term benefit to paracentesis in the management of acute primary angle-closure.

Summary for the Clinician

- Laser iridotomy is the definitive treatment for acute angle-closure; however, immediate paracentesis has been used to effectively and quickly lower IOP.
- Aseptic technique is mandatory when performing a paracentesis for acute angle-closure.

- Generally, the patient is premedicated with intravenous mannitol or acetazolamide and topical hypotensive medications.
- Paracentesis can be performed at the slit lamp or supine with an operating microscope and the V-Lance™ knife (20 Gauge, 1.3 mm) or a capsulotomy needle.
- In very shallow anterior chambers, extra care must be exercised to avoid hitting iris or the lens.
- There are many potential risks with paracentesis in the setting of acute angle-closure.
- A prospective, randomized trial is needed to study whether or not there is any benefit of immediately lowering the IOP in terms of long-term outcomes for the eye.

58.2 Is There a Role for Cataract Extraction in Acute Angle-Closure?

Lens removal during an acute angle-closure attack will relieve pupillary block [17] (but it will not relieve other mechanisms of angle-closure, such as plateau iris). In theory, lens extraction could effectively eliminate the risk of recurrence, limit damage to angle structures by opening up the anterior chamber angle, and avoid progression to chronic angle-closure glaucoma (CACG) [1, 2, 9–12, 17–28].

Two published studies [9, 10] found large IOP reductions following phacoemulsification for acute primary angle-closure. However, prospective, randomized studies comparing early cataract extraction with iridotomy are needed to answer whether lens removal is warranted in terms of long-term benefits (visual acuity and visual field preservation). Lam et al. showed that at 6 months following phacoemulsification, which was performed within 7 ± 3 days of medically aborting the acute angle-closure attack, there was a beneficial effect on IOP [1]. The authors cautioned that the risks of cataract extraction in the setting of an inflamed eye had to be weighed against the benefits. They found the surgical circumstances to be difficult due to corneal edema, shallow anterior chambers, existence of posterior synechiae, difficult-to-dilate pupils because of atrophic and atonic irides, and zonules that were weaker than usual. All of the above variables increased the risk of surgery. Published data from Lai et al. shows no clear correlation between IOP and extent of angle-closure after cataract extraction [12]; some eyes with only 90° of synechial closure required glaucoma medications postoperatively to control pressure, while other eyes with over 270° of PAS did not. The authors explained that in some eyes with open angles, the trabecular meshwork may be dysfunctional and there may be changes in aqueous production following cataract surgery.

If cataract extraction is to be performed shortly following acute angle-closure, a number of steps are necessary to ensure the best possible outcome for the patient. First, IOP should be lowered as much as possible to help clear corneal edema. Our experience has shown that topical sodium chloride 5 % solution and ointment can greatly decrease edema. IOP-lowering medications remain important and topical steroids should be used frequently to quiet the eye. Second, skillful technique is required for phacoemulsification on these eyes since the anterior chamber is shallow providing less operating room within which to maneuver. More care must be paid to avoid surge. Generous use of viscoelastic is necessary to protect the corneal endothelium and to separate posterior synechiae. Pupil dilating hooks can be used if necessary. Manipulation of the atonic and atrophied iris should be very gentle to avoid an excessive postoperative inflammatory response [1]. Third, intensive follow-up is necessary.

Gonioscopy or ultrasound biomicroscopy (UBM) examination is helpful to identify the extent of angle-closure before cataract extraction. In our Ophthalmic Center, phacotrabeculectomy plus intraocular lens (IOL) implantation is recommended for angles with ≥180° of angle-closure, while phacoemulsification plus IOL only

is performed on eyes with <180° of angle-closure [11]. This practice guideline has been used in China for the last decade.

Although to date there are no randomized, prospective, comparative studies on cataract extraction for CACG in terms of progression of visual field loss, cataract or lens extraction by phacoemulsification appears to be promising in terms of preventing progression to CACG after acute primary angle-closure. In terms of timing, waiting longer between acute closure and cataract extraction may be safest. Lam et al. have suggested that approximately 4 weeks be allowed to pass after aborting an acute attack. This time frame allows inflammation to settle, while usually IOP is still low due to low aqueous humor production [1]. Further studies are underway to define the role and best timing of phacoemulsification in acute primary angle-closure.

Summary for the Clinician

- Phacoemulsification is an option in the treatment of angle-closure.
- Phacoemulsification on an eye recently post-acute angle-closure attack is more technically challenging due to corneal edema, inflammation, atrophic iris, poorly dilating pupil, and shallow anterior chamber.
- Waiting for at least 4 weeks to pass from resolution of the acute angle-closure attack to phacoemulsification is recommended.
- Gonioscopy or UBM examination is important to perform before surgical treatment. In our Ophthalmic Center, phacotrabeculectomy is recommended for angles closed ≥180°, while phacoemulsification alone is recommended for angle-closure <180°.

58.3 How Should Angle-Closure Due to Phacomorphic Glaucoma or Loose Zonules Be Managed?

Phacomorphic glaucoma is lens-induced secondary angle-closure glaucoma. It can be caused by an increasingly large, mature cataract, or loose zonules. Loose or weak zonules may result in phacodonesis, lens subluxation, or dislocation, which can cause the lens to move forward and increase pupillary block [29–31].

The initial treatment of phacomorphic glaucoma is similar to that of PACG. IOP-lowering agents are administered to immediately reduce the IOP. Miotics, however, should be avoided as they will worsen the situation. Mydriatic-cycloplegic drops may relieve the pupillary block by dilating the pupil and tightening the loose zonules [30, 31]. A laser iridotomy is an appropriate next step to relieve the pupillary block if cataract extraction is impossible or in younger patients without nuclear sclerosis [29–32]. There is increasing evidence that immediate argon laser peripheral iridoplasty may be safe and effective as first-line treatment of acute phacomorphic angle-closure [33–35].

Surgical removal of the lens should be performed if visually significant cataract exists or if subluxation of the lens is causing uncontrollable IOP elevation. Various procedures have been reported in the setting of phacomorphic glaucoma: phacoemulsification alone, extracapsular cataract extraction alone, cataract extraction with IOL implantation or with glaucoma surgery, or pars plana vitrectomy and lensectomy [29–31, 36–38]. Phacoemulsification in the setting of loose zonules poses a higher than average risk of vitreous loss and/or need for placement of the IOL outside the capsule.

Surgery is best timed for when the eye is minimally inflamed, the cornea is clear, and IOP is controlled to a safe level for surgery [29, 30]. In order to achieve the best surgical outcome, some practical tips are given: (1) maintain an appropriate IOP level during the operation; (2) ensure wide dilation of the pupil and a continuous curvilinear capsulorhexis (CCC) greater than 6 mm;

(3) avoid surge during phacoemulsification so that the anterior chamber depth remains stable; (4) use lower ultrasound power and vacuum than you might normally use; (5) use a capsular tension ring to increase the safety and efficacy of surgery [39, 40]. Capsular tension rings have been found to improve both intraoperative support and postoperative IOL centration.

Repeated attacks of pupillary block may cause progressive PAS formation and chronic angle-closure. Gonioscopy or UBM examination can be helpful. If the angle is closed and IOP cannot be controlled, glaucoma surgery combined with cataract extraction is recommended [30]. Vitreous prolapse is frequently encountered during these operations. Postoperative complications include shallow anterior chamber, malignant glaucoma, and filtering bleb failure due to vitreous occlusion.

Summary for the Clinician

- Phacomorphic glaucoma is a form of pupillary block glaucoma that is aggravated by miotics but relieved by mydriatic-cycloplegic drops.
- Laser iridotomy or laser iridoplasty have been shown to help in phacomorphic glaucoma.
- Cataract extraction can be curative in phacomorphic glaucoma if permanent synechiae have not formed.
- Phacoemulsification is technically more challenging in phacomorphic glaucoma due to potentially loose zonules.

58.4 In Routine Cataract Surgery Where the Patient Has an Occludable Angle, Should LPI Be Performed Before Cataract Extraction or Can One Proceed Directly to Cataract Surgery?

This question has been debated by glaucoma specialists. An occludable angle is described as a narrow angle configuration without IOP elevation or angle synechiae. Some advocate an LPI prior to cataract surgery so that a peripheral retinal exam can be safely performed and to avoid the risk of acute angle-closure occurring as surgery is about to begin. Others advocate going straight to cataract extraction. Peripheral retinal examination can be done by B-scan ultrasound to rule out retinal detachments. If acute angle-closure occurs intraoperatively prior to cataract removal, a surgical iridectomy can be promptly performed so that the lens can be removed safely without elevated eye pressure.

It has been demonstrated that laser iridotomy can result in dramatic changes of the iris profile in pure pupil-block. One study of predominantly Chinese people with narrow angles found that LPI produced a significant increase in angle width [18]. However, iridotomy is often ineffective in preventing angle-closure in "pure" plateau iris [18]. The risk of closure depends on the height of the plateau and the width of the "gutter" between the peripheral iris and trabecular meshwork.

No published data shows that lens extraction in an eye with occludable angles is beneficial in preventing synechial closure or development of angle-closure glaucoma; however, there is accumulating evidence from UBM, anterior segment optical coherence tomography, and Schemipflug photography that cataract extraction can significantly deepen the anterior chamber and widen the drainage angle [1, 2, 9–12, 17–28]. In PACG patients with coexisting cataract, phacoemulsification can significantly reduce IOP, improve visual acuity, and decrease the requirement for topical glaucoma medications [9–12, 17–28]. Previous studies have also demonstrated that cataract extraction can increase the outflow of aqueous humor in angle-closure glaucoma [11, 25]. Although the literature has yet to show a long-term benefit of cataract extraction in eyes with occludable angles, it does seem biologically plausible that this procedure might help these eyes.

Thus, proceeding directly to cataract surgery by phacoemulsification in an eye with an occludable angle may achieve more benefit than performing an LPI before cataract extraction. However, published randomized controlled clinical trials are needed to definitively address this issue.

Summary for the Clinician

- There is no published data to support the idea of proceeding directly to cataract extraction or to perform an LPI prior to cataract surgery in patients with occludable angles.
- Removal of the lens may reduce the risk of acute attack, deepen the depth of anterior chamber, and widen the angle, thereby lowering the risk of progression from occludable angle to angle-closure glaucoma.

References

1. Lam DS, Tham CC, Lai JS, et al. Current approaches to the management of acute primary angle-closure. Curr Opin Ophthalmol. 2007;18:146–51.
2. Congdon NG, Friedman DS. Angle-closure glaucoma: impact, etiology, diagnosis, and treatment. Curr Opin Ophthalmol. 2003;14:70–3.
3. Lam DS, Lai JS, Tham CC, et al. Argon laser peripheral iridoplasty versus conventional systemic medical therapy in treatment of acute primary angel-closure glaucoma: a prospective, randomized, controlled trial. Ophthalmology. 2002;109:1591–6.
4. Lai JS, Tam CC, Chua JK, et al. To compare argon laser peripheral iridoplasty (ALPI) against systemic medications in treatment of acute primary angle-closure: mid-term results. Eye. 2006;20:309–14.
5. Lam DS, Chua JK, Tham CC, et al. Efficacy and safety of immediate anterior chamber paracentesis in the treatment of acute primary angle-closure glaucoma: a pilot study. Ophthalmology. 2002;109:64–70.
6. Carnahan MC, Platt LW. Serial paracenteses in the management of acute elevations of intraocular pressure. Ophthalmology. 2002;109:1604–6.
7. Pong JC. Anterior chamber paracentesis in patients with acute elevation of intraocular pressure. Graefes Arch Clin Exp Ophthalmol. 2008;246:463–4.
8. Arnavielle S, Creuzot-Garcher C, Bron AM. Anterior chamber paracentesis in patients with acute elevation of intraocular pressure. Graefes Arch Clin Exp Ophthalmol. 2007;245:345–50.
9. Jacobi PC, Dietlein TS, Luke C, et al. Primary phacoemulsification and intraocular lens implantation for acute angle-closure glaucoma. Ophthalmology. 2002;109:1597–603.
10. Zhang MZ, Lim ASM, Wong TY. A pilot study of lens extraction in the management of acute primary angle-closure glaucoma. Am J Ophthalmol. 2003;135:534–6.
11. Zhang X, Teng L, Ge J, et al. The clinical outcomes of three surgical managements on primary angle-closure glaucoma. Yan Ke Xue Bao. 2007;23:65–74.
12. Lai JS, Tam CC, Chan JC. The clinical outcomes of cataract extraction by phacoemulsification in eyes with primary angle-closure glaucoma (PACG) and co-existing cataract: a prospective case series. J Glaucoma. 2006;15:47–52.
13. Cheung CM, Durrani OM, Murray PI. The safety of anterior chamber paracentesis in patients with uveitis. Br J Ophthalmol. 2004;88:582–3.
14. Van der Lelij A, Rothova A. Diagnostic anterior chamber paracentesis in uveitis: a safe procedure? Br J Ophthalmol. 1997;81:976–9.
15. O'Rourke J, Taylor DM, McDonald P, et al. An aqueous paracentesis pipet. Ophthalmic Surg. 1991;22:166–7.
16. Helbig H, Noske W, Kleineidam M, et al. Bacterial endophthalmitis after anterior chamber paracentesis. Br J Ophthalmol. 1995;79:866.
17. Allingham RR. Shields' textbook of glaucoma. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 217–34.
18. He M, Foster PJ, Johnson GJ, et al. Angle-closure glaucoma in East Asian and European people. Different diseases? Eye. 2006;20:3–12.
19. Lowe RF. Aetiology of the anatomical basis for primary angle-closure glaucoma. Biometrical comparisons between normal eyes and eyes with primary angle-closure glaucoma. Br J Ophthalmol. 1970;54:161–9.
20. Lowe RF. Clinical types of primary angle-closure glaucoma. Aust N Z J Ophthalmol. 1988;16:245–50.
21. Kim YY, Jung HR. Clarifying the nomenclature for primary angle-closure glaucoma. Surv Ophthalmol. 1997;42:125–36.
22. Spaeth GL. The clinical outcomes of cataract extraction by phacoemulsification in eyes with primary angle-closure glaucoma (PACG) and co-existing cataract: a prospective case series. J Glaucoma. 2006;15:346.
23. Ge J, Guo Y, Liu Y, et al. Preliminary clinical study on the management of angle-closure glaucoma by phacoemulsification with foldable posterior chamber intraocular lens implantation. Chin J Ophthalmol (Zhonghua Yan Ke Za Zhi). 2001;37:355–8.
24. Hayashi K, Hyashi H, Nakao F, et al. Effect of cataract surgery on intraocular pressure control in glaucoma patients. J Cataract Refract Surg. 2001;27:1779–86.
25. Kim DD, Doyle JW, Smith MF. Intraocular pressure reduction following phacoemulsification cataract extraction with posterior chamber lens implantation in glaucoma patients. Ophthalmic Surg Lasers. 1999;30:37–40.
26. Nonaka A, Kondo T, Kikuchi M, et al. Cataract surgery of residual angle-closure after peripheral laser iridotomy. Ophthalmology. 2005;112:974–9.
27. Pereira FA, Cronemberger S. Ultrasound biomicroscopic study of anterior segment changes after phacoemulsification and foldable intraocular lens implantation. Ophthalmology. 2003;110:1799–806.

28. Leung CK, Chan WM, Ko CY, et al. Visualization of anterior chamber angle dynamics using optical coherence tomography. Ophthalmology. 2005;112:980–4.
29. Salmon JF, Kanski JJ. Glaucoma: a colour manual of diagnosis and treatment. 3rd ed. Edinburgh: Butterworth Heinemann; 2004. p. 95–7.
30. Minckler DS. Glaucoma associated with lens disorders. In: Eid TM, Spaeth GL, editors. The glaucomas: concepts and fundamentals. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 160–71.
31. Sowka J. Phacomorphic glaucoma: case and review. Optometry. 2006;77:586–9.
32. Tomey KF, Al-Rajhi AA. Neodymium: YAG laser iridotomy in the initial management of phacomorphic glaucoma. Ophthalmology. 1992;99:660–5.
33. Thyagarajan S. Immediate argon peripheral iridoplasty (ALPI) as initial treatment phacomorphic glaucoma: a safe and cost-effective treatment? Eye. 2006;20:1323.
34. Tham CC, Lai JS, Poon AS, et al. Immediate argon laser peripheral iridoplasty (ALPI) as initial treatment for acute phacomorphic angle-closure (phacomorphic glaucoma) before cataract extraction: a preliminary study. Eye. 2005;19:778–83.
35. Yip PP, Leung WY, Hon CY, et al. Argon laser peripheral iridoplasty in the management of phacomorphic glaucoma. Ophthalmic Surg Lasers Imaging. 2005;36:286–91.
36. Dada T, Kumar S, Gadia R, et al. Sutureless single-port transconjunctival pars plana limited vitrectomy combined with phacoemulsification for management of phacomorphic glaucoma. J Cataract Refract Surg. 2007;33:951–4.
37. Das JC, Chaudhuri Z, Bhomaj S, et al. Combined extracapsular cataract extraction with Ahmed glaucoma valve implantation in phacomorphic glaucoma. Indian J Ophthalmol. 2002;50:25–8.
38. Rao SK, Padmanabhan P. Capsulorhexis in eyes with phacomorphic glaucoma. J Cataract Refract Surg. 1998;24:882–4.
39. Hasanee K, Butler M, Ahmed II. Capsular tension rings and related devices: current concepts. Curr Opin Ophthalmol. 2006;17:31–41.
40. Yang J, Lu Y, Luo Y, et al. Clinical efficacy of management of zonular abnormalities with capsular tension ring: a two-year follow-up study. Chin J Ophthalmol (Zhonghua Yan Ke Za Zhi). 2007;43:519–24.

Complications: Hypotony

59

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Core Messages

- The clinical manifestations of acute and chronic postoperative hypotony are different.
- Hypotony is usually defined as intraocular pressure (IOP) less than 6 mmHg, but some eyes do tolerate an IOP at this low pressure without vision changes.
- Certain eyes are at greater risk for hypotony-induced complications.
- Treating hypotony requires identifying the cause of the low IOP.

59.1 What Are the Options in the Treatment of Early Postoperative Hypotony?

As much as glaucoma specialists desire low intraocular pressure (IOP) in their patients, the ocular effects of an IOP that is "too low" present an even greater risk to vision. Indeed, hypotony has profound effects on the function and structure of the eye. Hypotony is typically defined as an IOP less than 6 mmHg; however, some eyes tolerate this pressure without any untoward effects, while others develop hypotony maculopathy with decreased vision. Penetrating glaucoma surgery (such as a trabeculectomy or a drainage device implant) is one of the more common causes of hypotony, and therefore, hypotony should always be discussed during informed consent. Nonpenetrating surgery is much less likely to induce hypotony, although it may also be less likely to achieve a very low target pressure.

Determining the cause of early postoperative hypotony is essential in directing specific treatment (see Table 59.1). Immediately after surgery, a bleb may overfilter due to an excessively large sclerostomy, loose scleral flap closure, or poor conjunctival closure that leads to a wound leak. Other less common causes of early postoperative hypotony include a cyclodialysis cleft, retinal hole, or retinal detachment.

Hypotony in the early postoperative period after trabeculectomy can be avoided by meticulous surgery. Each step of the procedure is important. Cautious use of antifibrotics to avoid early postoperative hypotony is important, especially in high-risk eyes such as high myopes, aphakes, and those with a prior vitrectomy. Limbal- or fornix-based conjunctival flaps must be carefully sutured to prevent leakage. With drainage implants, the same principles of meticulous surgery apply. For example, the track through which the tube enters the anterior chamber should be large enough to pass the tube, but tight enough to avoid leaks around the tube; ideally, it is not larger than a 22- or 23-gauge needle track.

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Table 59.1 Causes of postoperative hypotony

Wound leak
Bleb leak
Large scleral fistula
Overfiltering bleb
Cyclodialysis cleft
Choroidal effusion
Retinal detachment
Cyclodestruction

In nonvalved drainage devices, the tube must be temporarily obstructed with either a rip-cord suture or tied off to prevent early hypotony.

59.1.1 Compression Sutures

Excessive aqueous outflow and hypotony may be associated with a very large, diffuse bleb. In some patients, this is associated with ocular irritation and blurred vision. These patients can be observed without intervention if complications do not ensue. As postoperative wound healing takes place in the first postoperative weeks, there is usually increasing resistance to aqueous flow resulting in the gradual IOP elevation and shrinkage of the bleb. Alternatively, compression sutures can be used to treat blebs that are leaking or painful. The purpose of the compression suture is to wall off the section that is leaking in order for it to heal. A 9–0 nylon suture is passed through the peripheral cornea, parallel to the limbus. The suture is then draped upward over the bleb and passed through conjunctiva 2–4 mm posterior to the bleb, in a direction parallel to the limbus. The knot is buried in the peripheral cornea. When the desired effect is achieved a few weeks later, the suture is removed.

59.1.2 Anterior Chamber Reformation

Hypotony can manifest with a flat or shallow anterior chamber. In hypotony, if the chamber is flat with lens to cornea touch, the anterior chamber should be reformed immediately to prevent corneal decompensation. Viscoelastic on a blunt cannula is injected into the anterior chamber through a paracentesis, performed at the time of surgery or created postoperatively. In either case, caution is advised not to damage iris or lens. A super sharp or 25-gauge needle can be used to accomplish this, aiming the needle over the iris. The anterior chamber can be completely filled with viscoelastic. Precautions against infection using povidine-iodine prep of the eyelashes and topical antibiotics are also necessary.

Occasionally, the anterior chamber will flatten again. Viscoelastic reformation of the anterior chamber can be performed multiple times, but if the chamber continues to quickly reflatten a more permanent solution must be considered, such as returning to the operating room to revise the trabeculectomy. If the anterior chamber is shallow but not flat, a course of cycloplegics can be tried. This can dramatically deepen the chamber within an hour as the ciliary body rotates and the lens shifts posteriorly. The patient can be sent home with cyclogyl, homatropine, or atropine and should be followed up within a couple of days to recheck the anterior chamber depth.

59.1.3 Choroidal Drainage

Hypotony can be accompanied by serous choroidal effusion. This tends to occur in elderly patients because their sclera is stiff and less likely to buckle with low pressure. In the Collaborative Initial Glaucoma Treatment Study, 11 % of the 300 patients who underwent trabeculectomy experienced a choroidal effusion [1]. The treatment for choroidal effusion is initially directed at finding and treating the cause of the hypotony to achieve a more physiologic IOP. A small, localized effusion in the first postoperative week may not require additional therapy, as these tend to be self-limited. For patients with symptomatic or prolonged effusions, draining the choroidal effusion may be necessary. Indications for drainage are (1) flat chamber, (2) “kissing” choroidals where retina to retina contact may lead to fibrin adherence of the retina, and (3) persistence after treating with

cycloplegics and topical steroids if the choroidals are causing a visual disturbance [2]. In nonhemorrhagic effusions, surgical drainage can be performed after a trial of cycloplegics and steroids if they do not provide any resolution.

After identifying and treating the cause of the hypotony, the effusion fluid is released by creating a scleral cut-down over the site where the choroidal effusion is most apparent. The conjunctiva is first opened in the area of intended scleral cut-down. A radial scleral incision to half-scleral thickness is made with a sharp blade approximately 3 mm from the limbus. The incision is then slowly deepened until the suprachoroidal space is reached. The incision can then be enlarged with a Kelley punch or with cautery. This will allow drainage of a straw or amber-colored fluid. Drainage of the fluid can be helped by compression of the sclera with a cotton swab; some surgeons will place a cyclodialysis spatula into the suprachoroidal space if there is no drainage so as to break up loculation that may be preventing fluid outflow, but this must be done gently and not more than a few millimeters from the incision. The scleral incision is left open but the conjunctival incision should be closed. This procedure is facilitated by placing an infusion probe through the limbus into the anterior chamber to maintain sufficient IOP. It is often necessary to place a second sclerostomy site in a different quadrant to help drain the loculated fluid.

Hemorrhagic choroidal effusions are more serious. Vision is compromised, pain may be evident, and retinal complications may ensue. Breakthrough bleeding into the vitreous is a vision-threatening event that compromises retinal integrity. Caution is advised when intervening; before draining a hemorrhagic effusion, one must allow 2–3 weeks to pass for the blood clot to lyse.

59.1.4 Repairing Wound Leaks

A conjunctival wound leak needs to be addressed if it is persistent and causing hypotony. Patching or applying a soft contact lens is an option often discussed in texts but seldom effective. Glues, superglue, or fibrin glue can be useful in a localized area of conjunctival exposure. A definitive approach requires additional sutures (10–0 nylon on a tapered non-cutting needle) placed adjacent to the site of leakage.

59.1.5 Resuturing of Trabeculectomy Flap

If hypotony persists as a problem, and the etiology is felt to be overfiltration through a loosely tied scleral flap, a return to the operating room to resuture the flap more tightly is the best course of action. Sutures should be tied more tightly than usual to raise the pressure and reverse side effects of hypotony. If the pressure is above the target, once the eye anatomically returns to normal, and there has been sufficient time for wound healing to occur, then suture lysis can be performed in an attempt to lower the pressure again. There is a risk of returning to a hypotonous state if this maneuver is done too soon.

Summary for the Clinician

- The key to treating hypotony is identifying and treating its underlying cause.

59.2 If There Is Hypotony Maculopathy, What Should Be Done to Manage It?

Long-term chronic hypotony has a profound effect on the structure and function of the eye. Shrinkage of the globe (as determined by measurement of axial length), corneal folds, cataract development or progression, and hypotony maculopathy are manifestations of chronically low IOP. Hypotony maculopathy is recognized by choroidal folds and/or retinal striae in the setting of low pressure. Hypotony maculopathy will

often affect younger patients and high myopes whose sclera is less rigid and more likely to fold and buckle with low pressure [3]. If left untreated, this will result in permanent vision loss. It is recommended that surgical intervention should only take place if hypotony maculopathy persists beyond 3 months, since after this time it becomes less likely that visual recovery will occur.

Summary for the Clinician

- Younger patients and myopes are at higher risk for hypotony maculopathy.
- Surgical intervention should occur to reverse hypotony if maculopathy persists beyond 3 months.

59.3 How Do I Perform Cataract Surgery in the Setting of Hypotony?

Intraocular lens calculation in eyes with cataract and chronic hypotony may be challenging. The hypotonous eye is often smaller than the fellow eye [4]. Complicating matters, cataract surgery can alter the IOP and change the postoperative axial length and refraction. It is difficult to predict if and how much a given eye's axial length will change. If a higher IOP is desired, reducing post-cataract steroid treatment can encourage inflammation leading to scarring and contraction of the bleb [5]. Sometimes pressurization of the eye during phacoemulsification can enlarge the bleb leading to lower postoperative IOP.

It is preferable to use optical axial length measurement rather than A-scan contact or immersion techniques as the latter can induce undesired artifacts. Hypotony and large blebs can induce corneal astigmatism [6]. Variable keratometry readings are common in hypotonous eyes. It is important to evaluate corneal topography to ensure that any measured astigmatism is regular before attempting to correct it with a toric lens.

The hypotonous eye creates challenges during the surgical procedure as well. Incision construction is more difficult in a hypotonous eye, which may necessitate suturing the wound at the end of the case. The use of viscoelastic to firm up the eye improves wound construction. The use of dispersive viscoelastic, especially if placed near any ostium, helps maintain the anterior chamber and prevent overfiltration into the bleb. Femtosecond laser-assisted cataract surgery is not suggested in hypotonous eyes as corneal folds can lead to impaired capsulorhexis creation and the required docking can compromise the previous glaucoma surgery.

Although cataract surgery in hypotonous eyes can be difficult, an understanding of the difficulties and possible outcomes can help in preoperative planning and patient counseling.

Summary for the Clinician

- Intraocular lens calculation can be challenging in an eye with hypotony because the axial length decreases.
- Intraocular lens calculations should be performed before glaucoma surgery in phakic eyes.

59.4 How Can I Manage Late Hypotony Due to a Scleral Melt?

A scleral melt will present with hypotony, but the actual melt may not be realized until one is in the operating room, and a full thickness hole is exposed by dissection of the conjunctiva. Treating a scleral melt requires careful preparation. If done poorly, hypotony may persist. If done properly, IOP may rise with ensuing glaucoma. Repair requires fresh conjunctiva and a scleral graft or tutoplast patch graft. I approach this with a traction suture through the superior cornea, a paracentesis to place viscoelastic to firm up the eye, excision of necrotic/ischemic conjunctiva or

scleral flaps, placing a donor scleral graft, followed by water-tight conjunctival closure. The scleral flap and adjacent sclera can be very friable and difficult to suture in cases of melt. Extra-long passes of the suture must be made to anchor sutures to normal tissue. Nondissolving suture should be used, as tension over the patch graft will be maintained for a much longer period of time.

Late onset hypotony is often more insidious in effect and more complicated to treat. It usually is a result of ischemic, necrotic conjunctiva, a scleral melt, or a combination of the two problems. The use of antifibrotics, especially mitomycin, has contributed greatly to this problem by irreversibly damaging cell function. Clinically, these patients present with decreased acuity from hypotony-induced complications, including maculopathy and shrinkage of the globe. More extensive conjunctival dehiscence or thinning will require surgical revision either with fresh tissue from above or grafting. A scleral melt may necessitate a scleral patch graft. Autologous blood injection is ineffective in this situation.

Summary for the Clinician

- Additional antifibrotics should be avoided.
- Tight closure over the area of scleral melt is necessary using either a scleral patch graft or pericardial patch graft to create a new scleral wall.
- Suture bites should include healthy scleral tissue of the patient's eye.
- Good conjunctival coverage is also necessary—a conjunctival autograft can be used in case of scarred or inadequate conjunctiva.
- Inadequate closure will result in continued hypotony, whereas successful closure often results in very high pressures.

59.5 Which Patients Are at Risk for Hypotony?

In the early postoperative period, patient groups particularly at risk for hypotony include the elderly, aphakes, those with systemic vascular disease (such as hypertension or diabetes) or prior vitrectomy, and patients on anticoagulants. People with high myopia have a greater chance of hypotony maculopathy following glaucoma filtration surgery. In particular, young high myopes have a thinner, less rigid scleral wall, which tends to collapse and exacerbate choroidal effusions. Sudden lowering of IOP, especially in the high-risk patient, may result in complications, such as shallow or flat anterior chambers and choroidal effusions. A less common but more serious complication would be an acute or delayed choroidal hemorrhage causing profound visual loss and severe ocular pain [7].

Summary for the Clinician

- Risk factors for hypotony include the elderly, aphakes, prior vitrecomy, high myopes, and systemic vascular disease.

References

1. Jampel HD, Musch DC, Gillespie BW, et al. Perioperative complications of trabeculectomy in the collaborative initial glaucoma treatment study (CIGTS). Am J Ophthalmol. 2005;140:16–22.
2. WuDunn D, Ryser D, Cantor LB. Surgical drainage of choroidal effusions following glaucoma surgery. J Glaucoma. 2005;14:103–8.
3. Costa VP, Arcieri ES. Hypotony maculopathy. Acta Ophthalmol Scand. 2007;85:586–607.
4. Francis BA, Wang M, Lei H, et al. Changes in axial length following trabeculectomy and glaucoma drainage device surgery. Br J Ophthalmol. 2005;89:17–20.
5. Joyle JW, Smith MF. Effect of phacoemulsification surgery on hypotony following trabeculectomy surgery. Arch Ophthalmol. 2000;118:763–5.
6. Egrlimez S, Ates H, Nalcaci S, et al. Surgically induced corneal refractive change after glaucoma surgery: nonpenetrating trabecular surgeries versus trabeculectomies. J Cataract Refract Surg. 2004;30:1232–9.
7. Tuli SS, WuDunn D, Ciulla TA, et al. Delayed suprachoroidal hemorrhage after glaucoma filtration surgery. Ophthalmology. 2001;108:1808–11.

Complications: Bleb Leaks

60

Philip P. Chen

Core Messages

- A bleb leak, early or late, is a potentially vision-threatening complication of glaucoma-filtering surgery.
- Early bleb leaks can be associated with bleb failure and should be treated promptly.
- Conservative measures for early bleb leaks include temporarily withholding corticosteroid drops, aqueous suppression, and bandage contact lens placement.
- In the early postoperative period, a briskly leaking hole or wound dehiscence may require suturing.
- Late bleb leaks are associated with bleb-related infection and endophthalmitis and may be associated with hypotony and poor vision. Because of these associations, they usually require treatment.
- Late leaks may be treated with conservative measures initially. Although the chance of successful closure of the leak is not high, there is little risk to intraocular pressure (IOP) control.
- More aggressive treatment for late bleb leaks may be necessary, ranging from autologous blood injection to bleb revision using conjunctival advancement, conjunctival flaps, or conjunctival autografting.
- Conjunctival advancement is perhaps the simplest procedure, but has probably the highest likelihood of loss of IOP control.

60.1 Does an Early Bleb Leak Need to Be Fixed?

Controversy exists regarding the effect of early postoperative bleb leaks on trabeculectomy outcomes. The Flourouracil Filtering Surgery Study found that early wound leaks were strongly associated with failure [31]. However, other authors have not found this association, though the number of leaks in their studies was small [1, 9, 18]. In my experience, the extent of early bleb leakage *does* affect trabeculectomy success. An incision line leak must be closed or the bleb will not form, conjunctival scarring will occur, and the bleb will eventually fail. However, small or pinpoint leaks often can heal spontaneously, or with the aid of conservative measures such as bandage contact lenses, without affecting long-term bleb success. Other potential complications

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of an early leak are anterior chamber shallowing and a route for the development of endophthalmitis. Management of the leak depends on the leak's cause and severity.

60.1.1 With a Small, Early Postoperative Bleb Leak, What Options Are Available to Help It Heal?

If the leak is small, for example, a pinpoint suture track leak or inadvertent perforation of the bleb with a needle that was not noted and repaired intraoperatively, a bandage contact lens may be placed on the eye along with prophylactic topical antibiotics [4]. In cases where the bleb tissue is not thin or friable, a light touch of cautery to the leak site may also encourage healing. To perform this procedure without creating new holes, the cautery unit is allowed to heat fully (Fig. 60.1) and then is allowed to cool briefly (Fig. 60.1) before being gently applied to the leaking area. A bandage lens is then applied and left in place for 3–14 days, depending on the leak size. Usually the frequency of topical corticosteroid drops is reduced, sometimes withholding them completely for at least a short time, while the contact lens is in the eye. In addition, the patient may have to use some form of topical aqueous suppressant at a reduced dose (e.g., timolol–dorzolamide combination once daily) to intermittently reduce aqueous flow through the leaking area and encourage healing, while still allowing periods of relatively normal aqueous production to encourage bleb formation. For limbus-based conjunctival flaps, an oversize contact lens must be used (Flexlens™, X-Cel Contacts, Duluth, GA) (Fig. 60.2). For

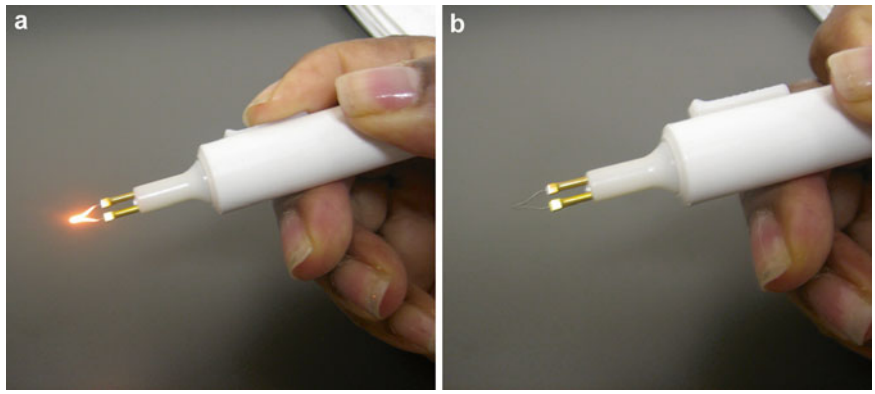

Fig. 60.1 A handheld cautery (high or low temperature unit) can be used to help a small early bleb leak. (**a**) The unit is heated until *red hot*. (**b**) The unit is allowed to cool slightly before applying to the conjunctiva

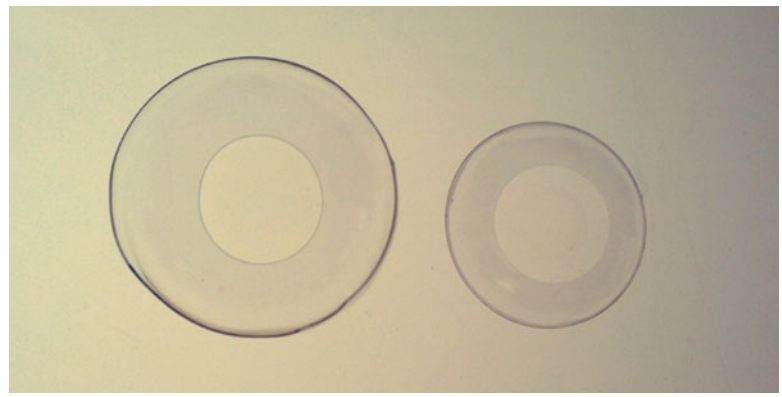

Fig. 60.2 Oversize (22.0 mm) bandage contact lens (*left*), compared with standard 14.0-mm bandage

fornix-based conjunctival flaps, a bandage contact lens of 14–16 mm diameter will cover the limbus adequately. Another potential solution for fornix-based conjunctival flaps is a pressure patch, but whether the pressure will be constantly applied to the correct location is uncertain.

If the leak persists at the next visit but is reduced in size and flow, the bandage lens should be replaced and left in place for up to twice the original time period, assuming the bleb is otherwise forming well and the anterior chamber remains deep. However, if the bleb appears flat, particularly in cases without intraoperative use of antifibrotics, suturing of the leak should be performed sooner rather than later to avoid outright bleb failure, using the technique described in Sect. 60.1.2 below. Autologous fibrin glue [3] is another possible treatment for leaks, although its use may be cumbersome.

60.1.2 With a Large/Brisk, Early Postoperative Bleb Leak, What Options Are Available to Help It Heal?

If there is a large, briskly flowing leak and a flat bleb is noted due to localized wound dehiscence, or if a smaller leak proves recalcitrant and the surrounding tissue is sufficiently robust to allow passage of a needle without cheese-wiring or expanding the leaking area, that area should be resutured with a 9–0 polyglactin or 10–0 nylon suture on a tapered blood vessel needle. A mattress stitch is generally sufficient to correct the problem, although if there is generalized laxity of the incision due to poor initial wound closure, a complete resuturing of the entire incision may be necessary.

A localized repair can be performed at the slit lamp in a cooperative patient under topical anesthetic. If this option is pursued, one should perform a povidone–iodine preparation of the eyelids, utilize pre- and postoperative antibiotic drops, and utilize an eyelid speculum. Light cautery using a handheld, battery-powered cautery unit prior to suturing may also encourage healing of the leak, using the technique described in Sect. 60.1.1 above. In some cases, a supine patient and an operating microscope may be necessary, either in a minor procedure room or in the operating room. Topical corticosteroids may be reduced in frequency or withheld for a short period of time and aqueous suppression may be employed as described in the section above to assist in leak closure. Laser suture lysis and/or bleb needling to obtain optimal intraocular pressure (IOP) control is frequently necessary after the leak has healed completely, even when antifibrosis agents such as mitomycin C (MMC) have been used intraoperatively, in my experience.

Another method to close a leak is to wall it off using a Palmberg-style compression stitch of 9–0 or 10–0 nylon under topical anesthesia in a minor procedure room or operating room [29]. This may be useful in cases where the bleb is very thin or cystic, even in the early postoperative period.

60.1.3 What Can I Do If the Leak Continues to Persist?

In some cases, typically in eyes with multiple trabeculectomies and/or bleb needling revisions using antifibrosis agents, an early postoperative leak occurs that proves resistant to healing with any of the above techniques. The tissue is likely too friable and/or acellular to repair the leak, or the edges of the wound have fully epithelialized and simple closure will not result in the desired healing result, even after freshening of the tissue edges. One technique that can be successful in such a situation is to excise the leaking area and suture an oversized autologous conjunctival graft, similar to what has been described for late bleb leaks (see Sect. 60.2.3 for details).

Summary for the Clinician

- Early bleb leaks can be due to poor wound closure or poor wound healing.
- Small early leaks can often be sealed with some combination of steroid withholding,

aqueous suppression, and bandage contact lens placement. These leaks rarely lead to bleb failure.

- Large early leaks or wound dehiscence usually requires suture placement, which sometimes can be done at the slit lamp but often requires an operating microscope. Such leaks can lead to bleb failure if not fixed promptly.

60.2 How Should I Treat a Late-Onset Bleb Leak?

Histopathological studies of eyes that have undergone trabeculectomy with MMC and subsequently developed bleb leaks and/or hypotony have shown attenuated and irregular epithelium and breaks in the basement membrane [14, 19, 35]. However, other antifibrosis agents (such as 5-fluorouracil [5-FU]) and full-thickness filtering procedures can result in the same clinical appearance. The thin epithelial surface presumably breaks down from repeated trauma incurred by eyelid blinking, resulting in a bleb leak. Localized drying of the tissue due to a relative paucity of goblet cells may contribute to the problem [14].

Late bleb leaks are not infrequent following trabeculectomy. Lamping et al. [24] reported that filtering surgery without antifibrosis agents resulted in a 2.3 % frequency of bleb leaks, with a mean onset of 3 years; after full-thickness procedures the rate was higher at 3.3 %. In the Fluorouracil Filtering Surgery Study, 8.6 % of 105 eyes treated with 5-FU developed late bleb leaks at an average of 22 months following surgery, while only 1.9 % of 108 eyes that underwent trabeculectomy without 5-FU experienced this complication at a mean of 45 months after surgery [13]. In a study of 525 eyes, Greenfield et al. [16] found leaks in 3.7 % of MMC trabeculectomies (including 5.9 % of MMC trabeculectomies without cataract extraction), 1.4 % of 5-FU trabeculectomies, and 2.6 % of filtering surgeries without antifibrosis agents. The Kaplan–Meier survival analysis estimated that 13 % of MMC blebs would be leaking by 5 years after surgery. Similarly, Debry studied 258 eyes that had undergone MMC trabeculectomies and estimated 17.9 % would have had a bleb leak at 5 years after surgery [12].

Late-onset bleb leaks are associated with many vision-threatening complications, including blebitis and bleb-related endophthalmitis [11, 37, 38]. Poor vision can result if a leak is associated with hypotony maculopathy, choroidal detachments, corneal folds or edema, or refractive error fluctuation. Additionally, some patients are bothered by the epiphora that is frequently associated with a bleb leak.

60.2.1 Conservative Treatments for Late Bleb Leaks

Conservative treatments may close the leak without affecting bleb function. Maximal aqueous suppression, consisting of a topical beta blocker, carbonic anhydrase inhibitor, and alpha agonist, should be instituted. A protective shield at bedtime may be used if inadvertent trauma while sleeping is considered to be a contributory etiology. Even in cystic avascular blebs, this regimen sometimes slows aqueous leakage enough to allow the epithelium to heal after several weeks to months of treatment. However, late recurrent bleb leaks are not uncommon in thin or cystic blebs.

Other conservative options include pressure patching or an oversized soft contact lens, either of which could be combined with aqueous suppression. It must be kept in mind that with high or large blebs a bandage lens often does not stay in place well. Symblepharon rings and collagen shields have been used in the same manner. Other methods of treatment, such as trichloroacetic acid, cyanoacrylate glue, and argon laser, have been described, but these options are unlikely to be effective in a thin cystic bleb. There is also the risk that their use could enlarge the preexisiting hole. Chronic use of topical antibiotics in eyes after trabeculectomy irrespective of the presence of a bleb leak, presumably as prophylaxis against possible infection, has been associated with bleb infection and is contraindicated [20].

Unfortunately, these approaches often fail to seal the leak, and further treatment becomes necessary. If the leak was found incidentally and there is good vision and no infection or hypotony, I might continue conservative treatments for several months. However, if there is a history of previous bleb infection, I would not use conservative treatments for more than a month. Burnstein et al. [8] compared the outcome of conservative treatment to bleb revision and found a significantly greater chance of failure in the group managed conservatively. Reasons for failure were persistent or recurrent leaks, bleb infection, endophthalmitis, and bleb dysesthesia. In total, only 12 of 37 eyes treated conservatively achieved a lasting, leak-free bleb without secondary complications.

60.2.2 Autologous Blood Injection

Another relatively simple treatment is intra- or peri-bleb autologous blood injection. The success of this treatment option is variable in bleb leaks [7, 25, 36]. It can be performed under topical anesthesia at the slit lamp in a cooperative patient. Because of the relative technical ease of this procedure and the overall low incidence of adverse events, I will typically try autologous blood injection prior to undertaking more extensive surgical revision. The patient's venous blood is drawn, and 0.5–1.0 ml of it is used for injection into or around the bleb. This technique can be combined with a bandage contact lens. Viscoelastic may be injected into the anterior chamber near the ostium prior to blood injection in order to prevent blood from trickling under the flap and into the anterior chamber, which can cause a hyphema and consequent visual loss. One potential side effect of using viscoelastic is an acute elevation of IOP.

60.2.3 Compression Sutures

Palmberg and Zacchei [29] described use of compression sutures of 9–0 or 10–0 nylon or polyglactin to repair bleb leaks, a technique that can be performed under topical anesthetic but requires an operating microscope. Leak recurrence remains a problem due to underlying bleb wall hypocellularity that is not affected in the long term.

60.2.4 Laser

Some authors have used the Nd:YAG laser in continuous wave-mode with some success to close leaks. Success is attributed to the inflammation caused by this laser in the underlying episclera and uveal tissue [15, 27]. This technique requires retrobulbar anesthesia and access to this uncommon type of Nd:YAG laser. Complications reported include creation of new bleb leaks, corneal edema, and cataract formation.

60.2.5 Surgical Bleb Revision

The treatment most likely to heal a bleb leak is surgical revision in the operating room. Several approaches have been described. One of the most straightforward is *direct conjunctival/Tenon's advancement*: a wide peritomy is made on each side of the bleb and the conjunctiva posterior to the bleb is mobilized sufficiently to allow advancement to the limbus. After excision of the leaking bleb, aqueous flow around the scleral flap is assessed. If the flow is felt to be too brisk, the scleral flap may be sutured, or a graft of Tenon's or donor sclera may be sutured over the flap. The conjunctiva is then directly sutured to the freshened limbus [6, 23, 26, 32, 39, 40]. Some surgeons suture the conjunctiva to a groove made in the cornea. A watertight conjunctival closure also can be achieved using a 10–0 nylon mattress suture directly in front of the scleral flap and 8–0 polyglactin wing sutures that bring the conjunctiva taut at the limbus. Sometimes a relaxing incision of the conjunctiva in the superior fornix is useful to mobilize the tissue, to allow suturing to the limbus without undue tension [28].

Most reports indicate that approximately 40 % of patients will need to use additional glaucoma medications after bleb revision by direct

advancement, and about 10 % will need further glaucoma surgery. Late failure of the bleb is a definite possibility; in one study, the probability of at least a qualified success (IOP controlled with medications) after conjunctival advancement was 72 % at 2 years, but fell to 15 % at 5 years by Kaplan–Meier survival analysis [2]. My experience with IOP control after bleb revision by direct conjunctival advancement has led me to apply MMC (0.4 mg/ml) in selected cases to the sclera posterior to the scleral flap and to the overlying Tenon's and conjunctiva, prior to suturing conjunctiva to the limbus. The area around the scleral flap, which is open to reverse flow of MMC into the anterior chamber, is protected with viscoelastic, which is also injected into the anterior chamber via a paracentesis incision. Subconjunctival injection of a small amount of MMC (0.05–0.2 ml of a 0.2 mg/ml dilution) could also be used and would avoid the issue of MMC entering the anterior chamber. Although applying MMC in a bleb revision for a leaking bleb may seem counterintuitive, I have found that the conjunctiva and Tenon's located posterior to the bleb is typically quite robust, and thin blebs or bleb leaks have not resulted from this technique.

Wilson et al. [41] reported on the use of a *free conjunctival autograft* in place of an excised bleb; others have also reported on this more technically demanding technique, which appears to result in better IOP control than conjunctival advancement [23, 30, 33]. Other techniques have been published that do not excise the preexisting bleb, but rather de-epithelialize it and cover it with conjunctiva that has been advanced from behind the bleb [10], or with an autologous conjunctival graft [17]. These reports also show better maintenance of IOP control postoperatively; however, they are not case-control or randomized controlled trials, so direct comparisons cannot be made.

Another technique of leak closure involves the use of *amniotic membrane*, which is placed over a leaking bleb to help seal the leak [22]. However, a randomized study found it to be inferior to conjunctival advancement [5]. A recent study found 15 of 17 eyes (88 %) with success using amniotic membrane without excision of the cystic bleb [34]. Another technique used by this author is placement of a *glaucoma drainage device in combination with closure of the old filtering surgery site* using donor sclera, a relatively lengthy but definitive operation.

Summary for the Clinician

- Late bleb leaks are not infrequent after successful filtering surgery—they occur in up to 13 % of cases using antimetabolite after 5 years of follow-up.
- Bleb leaks are usually related to thin, avascular blebs.
- Late leaks are associated with vision-threatening blebitis and endophthalmitis and should be treated.
- Depending on the leak severity and absence of associated complications (i.e., endophthalmitis, hypotony), conservative measures may be tried for several weeks or months to close the leak.
- Chronic use of topical antibiotics should be avoided, as this has been associated with development of endophthalmitis after trabeculectomy irrespective of bleb leakage.
- Autologous blood injection is a relatively noninvasive treatment, which may heal the leak, and is readily performed at the slit lamp.
- Surgical bleb revision may be necessary to stop a late bleb leak. Various techniques can successfully close a leak but often at the price of reduced IOP control.
- Some patients may require further glaucoma surgery following bleb revision.

60.3 What Can I Do to Decrease the Chances of a Future Bleb Leak?

The best method for dealing with late bleb leaks is to create blebs that are not prone to leaking. Some authors have shown that thicker,

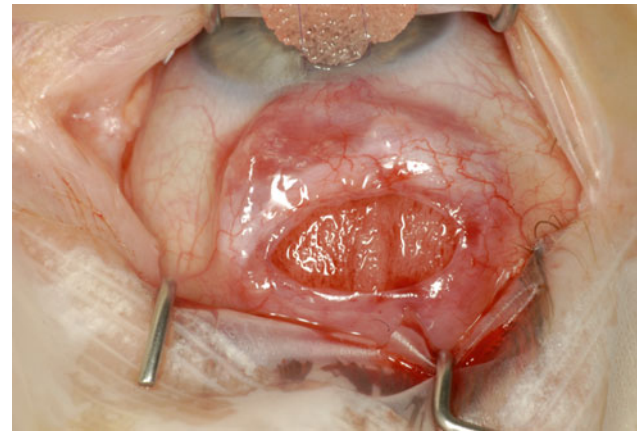

Fig. 60.3 Placement of two pieces of cellulose sponge soaked in mitomycin C, which extend beyond the edges of the conjunctival incision in a limbus-based trabeculectomy

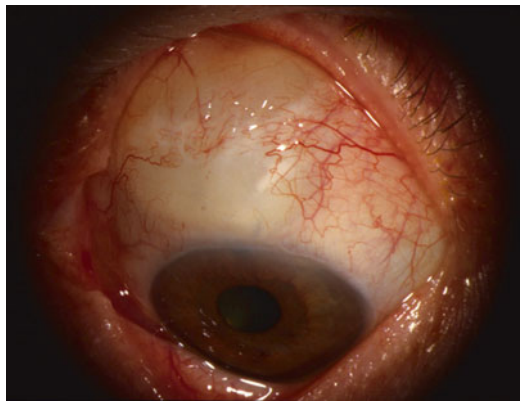

Fig. 60.4 The typical resulting bleb (note, not the same patient as Fig. 60.2) is relatively thick though not heavily vascularized, and aqueous flow extends posteriorly beyond the incision line

more diffuse blebs are more likely to develop in the setting of fornix-based trabeculectomies and use of antifibrosis agents over a large surface area (rather than focal application only over the scleral flap) [21]. Modifications that this author has employed with his limbus-based technique to create a more diffuse, thicker bleb are to use multiple large, thin sponges soaked in MMC that extend beyond the conjunctival incision and a meticulous single-layer closure with a 9–0 polyglactin suture on a tapered BV needle. This combination allows aqueous to more freely flow posteriorly past the conjunctival incision line and promotes formation of a larger, thicker, more diffuse bleb (Figs. 60.3 and 60.4).

Summary for the Clinician

- Techniques to prevent leak-prone blebs should be employed initially.
- Diffuse blebs are less likely to leak.
- A diffuse bleb can be promoted by applying antimetabotlite over a larger surface area and with fornix-based wounds.

References

1. AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 11. Risk factors for failure of trabeculectomy and argon laser trabeculoplasty. Am J Ophthalmol. 2002;134:481–98.
2. Al-Shahwan S, Al-Torbak AA, Al-Jadaan I, et al. Long-term follow up of surgical repair of late bleb leaks after glaucoma filtering surgery. J Glaucoma. 2006;15:432–6.
3. Asrani SG, Wilensky JT. Management of bleb leaks after glaucoma filtering surgery. Use of autologous fibrin tissue glue as an alternative. Ophthalmology. 1996;103:294–8.
4. Blok MD, Kok JH, van Mil C, et al. Use of the megasoft bandage lens for treatment of complications after trabeculectomy. Am J Ophthalmol. 1990;110:264–8.
5. Budenz DL, Barton K, Tseng SC. Amniotic membrane transplantation for repair of leaking glaucoma filtering blebs. Am J Ophthalmol. 2000;130:580–8.
6. Budenz DL, Chen PP, Weaver YK. Conjunctival advancement for late-onset filtering bleb leaks: indications and outcomes. Arch Ophthalmol. 1999;117:1014–9.
7. Burnstein A, WuDunn D, Ishii Y, et al. Autologous blood injection for late-onset filtering bleb leak. Am J Ophthalmol. 2001;132:36–40.

8. Burnstein AL, WuDunn D, Knotts SL, et al. Conjunctival advancement versus nonincisional treatment for late-onset glaucoma filtering bleb leaks. Ophthalmology. 2002;109:71–5.
9. CAT-152 Trabeculectomy Study Group, Grehn F, Holló G, et al. Factors affecting the outcome of trabeculectomy: an analysis based on combined data from two phase III studies of an antibody to transforming growth factor beta2, CAT-152. Ophthalmology. 2007;114:1831–8.
10. Catoira Y, Wudunn D, Cantor LB. Revision of dysfunctional filtering blebs by conjunctival advancement with bleb preservation. Am J Ophthalmol. 2000;130:574–9.
11. Chen PP, Gedde SJ, Budenz DL, et al. Outpatient treatment of bleb infection. Arch Ophthalmol. 1997;115:1124–8.
12. DeBry PW, Perkins TW, Heatley G, et al. Incidence of late-onset bleb-related complications following trabeculectomy with mitomycin. Arch Ophthalmol. 2002;120:297–300.
13. Fluorouracil Filtering Surgery Study Group. Five-year follow-up of the Fluorouracil Filtering Surgery Study. Am J Ophthalmol. 1996;121:349–66.
14. Francis BA, Du LT, Najafi K, et al. Histopathologic features of conjunctival filtering blebs. Arch Ophthalmol. 2005;123:166–70.
15. Geyer O. Management of large, leaking, and inadvertent filtering blebs with the neodymium: YAG laser. Ophthalmology. 1998;105:983–7.
16. Greenfield DS, Liebmann JM, Jee J, et al. Late-onset bleb leaks after glaucoma filtering surgery. Arch Ophthalmol. 1998;116:443–7.
17. Harris LD, Yang G, Feldman RM, et al. Autologous conjunctival resurfacing of leaking filtering blebs. Ophthalmology. 2000;107:1675–80.
18. Henderson HW, Ezra E, Murdoch IE. Early postoperative trabeculectomy leakage: incidence, time course, severity, and impact on surgical outcome. Br J Ophthalmol. 2004;88:626–9.
19. Hutchinson AK, Grossniklaus HE, Brown RH, et al. Clinicopathologic features of excised mitomycin filtering blebs. Arch Ophthalmol. 1994;112:74–9.
20. Jampel HD, Quigley HA, Kerrigan-Baumrind LA, et al. Risk factors for late-onset infection following glaucoma filtration surgery. Arch Ophthalmol. 2001;119:1001–8.
21. Jones E, Clarke J, Khaw PT. Recent advances in trabeculectomy technique. Curr Opin Ophthalmol. 2005;16:107–13.
22. Kee C, Hwang JM. Amniotic membrane graft for late-onset glaucoma filtering leaks. Am J Ophthalmol. 2002;133:834–5.
23. La Borwit SE, Quigley HA, Jampel HD. Bleb reduction and bleb repair after trabeculectomy. Ophthalmology. 2000;107:712–8.
24. Lamping KA, Bellows AR, Hutchinson BT, et al. Long-term evaluation of initial filtration surgery. Ophthalmology. 1986;93:91–101.
25. Leen MM, Moster MR, Katz LJ, et al. Management of overfiltering and leaking blebs with autologous blood injection. Arch Ophthalmol. 1995;113:1050–5.
26. Lin AP, Chung JE, Zhang KS, Chang MM, Orengo-Nania S, Gross RL, Chang PT. Outcomes of surgical bleb revision for late-onset bleb leaks after trabeculectomy. J Glaucoma. 2013;22:21–5.
27. Lynch MG, Roesch H, Brown RH. Remodeling filtering blebs with the neodymium: YAG laser. Ophthalmology. 1996;103:1700–5.
28. O'Connor DJ, Tressler CS, Caprioli J. A surgical method to repair leaking filtering blebs. Ophthalmic Surg. 1992;23:336–8.
29. Palmberg P, Zacchei AC. Compression sutures – a new treatment for leaking or painful filtering blebs. Invest Ophthalmol Vis Sci. 1996;37:S444.
30. Panday M, Shantha B, George R, Boda S, Vijaya L. Outcomes of bleb excision with free autologous conjunctival patch grafting for bleb leak and hypotony after glaucoma filtering surgery. J Glaucoma. 2011;20:392–7.
31. Parrish RK, Schiffman JC, Feuer WJ, et al. Prognosis and risk factors for early postoperative wound leaks after trabeculectomy with and without 5-fluorouracil. Am J Ophthalmol. 2001;132:633–40.
32. Radakrishnan S, Quigley HA, Jampel HD, Friedman DS, Ahmad SI, Congdon NG, McKinnon S. Outcomes of surgical bleb revision for complications of trabeculectomy. Ophthalmology. 2009;116:1713–8.
33. Schnyder CC, Shaarawy T, Ravinet E, et al. Free conjunctival autologous graft for bleb repair and bleb reduction after trabeculectomy and nonpenetrating filtering surgery. J Glaucoma. 2002;11:10–6.
34. Sethi P, Patel RN, Goldhardt R, Ayyala RS (2014) Conjunctival advancement with subconjunctival amniotic membrane draping technique for leaking cystic blebs. J Glaucoma. 2016;25:188–92
35. Shields MB, Scroggs MW, Sloop CM, et al. Clinical and histologic observations concerning hypotony after trabeculectomy with mitomycin C. Am J Ophthalmol. 1993;116:673–83.
36. Smith MF, Magauran III RG, Betchkal J, et al. Treatment of postfiltration bleb leaks with autologous blood. Ophthalmology. 1995;102:868–71.
37. Soltau JB, Rothman RF, Budenz DL, et al. Risk factors for glaucoma filtering bleb infections. Arch Ophthalmol. 2000;118:338–42.
38. Song A, Scott IU, Flynn Jr HW, et al. Delayed-onset bleb-associated endophthalmitis: clinical features and visual acuity outcomes. Ophthalmology. 2002;109:985–91.
39. Tannenbaum DP, Hoffman D, Greaney MJ, et al. Outcomes of bleb excision and conjunctival advancement for leaking or hypotonous eyes after glaucoma filtering surgery. Br J Ophthalmol. 2004;88:99–103.
40. Wadhwani RA, Bellows AR, Hutchinson BT. Surgical repair of leaking filtering blebs. Ophthalmology. 2000;107:1681–7.
41. Wilson MR, Kotas-Neumann R. Free conjunctival patch for repair of persistent late bleb leak. Am J Ophthalmol. 1994;117:569–74.

Complications: Blebitis

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Core Messages

- The presence of a bleb leak is associated with a significantly increased risk of bleb-related infections.
- Tube exposure is the most important risk factor for postoperative infections and endophthalmitis involving tube shunts.
- Topical antibiotics can be used for early blebitis.
- Intravitreal injections should be used if there are cells in the vitreous since this is considered an endophthalmitis.
- Pars plana vitrectomy can be considered for bleb-associated endophthalmitis since the organisms associated with this infection tend to be particularly virulent.
- Management of endophthalmitis in the setting of an exposed tube should be addressed promptly with antibiotics, repair, and/or removal of the exposed tube.

61.1 How Likely Is Blebitis and/or Endophthalmitis in the Presence of a Bleb Leak?

The development of bleb-related infections is a well-recognized complication of glaucoma-filtering surgery. Although bleb-related infections are multifactorial, the presence of a bleb leak is associated with a 20-fold increase in the risk of developing blebitis or bleb-related endophthalmitis [1]. The presence of a leak mechanistically contributes to a higher incidence of infection by reducing the conjunctival resistance against bacteria and/or by increasing the bacterial load. The odds of an eye with a bleb-related infection having concomitant late-onset bleb leak are 25.8 times greater than a noninfected eye having a late-onset bleb leak [2].

It is imperative to inform patients with a bleb leak of the increased risk of bleb-related infections, and for the patients to report immediately the development of any symptoms of a

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leak or infection to his ophthalmologist. Bleb leaks in the setting of bleb-related infections can be managed conservatively at first; however, if the leak persists despite conservative treatment, surgical revision of the bleb should be considered.

Summary for the Clinician

- The presence of a bleb leak is associated with a 20-fold increased risk of developing a bleb-related infection.
- Patients should be informed of the increased risk and should immediately report any symptoms of a bleb-related infection to their ophthalmologist.
- Surgical revision of persistent bleb leaks in the setting of bleb-related infections must be considered if conservative measures fail.

61.2 How Likely Is Endophthalmitis in the Presence of anExposed GDD Tube or Plate?

Tube or plate exposure is a major risk factor for postoperative infections involving glaucoma drainage devices. In several well-documented reports, 66–100 % of eyes that developed endophthalmitis had tube exposure at the time of diagnosis [3–5]. Despite the advent of placing banked sclera, pericardium, or other fibrous tissue over the tube to prevent conjunctival erosion, tube exposure can still occur at any time postoperatively. The superior conjunctiva is particularly susceptible to thinning due to the constant mechanical rubbing by the upper eyelid during blinking [6]. Erosion is also more likely to occur in the setting of previously thinned or scarred conjunctiva or excessive tissue tension during wound closure. The conjunctival breach may extend posteriorly leaving the anterior aspect of the plate exposed as well. The proposed mechanism of endophthalmitis involves bacteria tracking down the tube into the eye or around the plate [6]. Prompt evaluation is warranted in every case of an exposed GDD tube or plate due to the deleterious consequences of endophthalmitis.

Summary for the Clinician

- A large percentage of eyes have tube exposure at the time of being diagnosed with endophthalmitis.
- Tube exposure, with or without conjunctival erosion, may occur at any time postoperatively.
- With tube or plate exposure, bacteria have direct intraocular access in or around the tube leading to a significantly increased risk of endophthalmitis.

61.3 What Topical Antibiotics Should I Use in Blebitis?

If the patient seems (1) capable of adhering to an aggressive topical regimen, (2) able to return for frequent clinical monitoring, and (3) if the case is not severe (e.g., less than 3+ cells in the anterior chamber), then the patient can be treated in an outpatient setting. It is generally acceptable to use topical fourth-generation fluoroquinolones, such as gatifloxacin 0.3 % and moxifloxacin 0.5 % [7]. On initial presentation, the antibiotics should be dosed every hour (around the clock). Oral third- and fourth-generation fluoroquinolones can be added in conjunction with topical medications, as they do have some intraocular/vitreal penetration [2, 8]; fourth-generation oral fluoroquinolones have better intraocular penetration compared with oral third-generation fluoroquinolones [9–11]. Alternatively, fortified topical drops of cefazolin 5 % (or vancomycin 2.5 %) and tobramycin 1.5 % can be considered and dosed every hour, each separated by 30 min, so that the patient receives a dose of the first or second medication every 30 min [7].

If the patient seems unable to adhere to a topical regimen and frequent follow-up or has a severe anterior chamber reaction (3+ or greater cellular reaction in the anterior chamber), then the clinician should consider admitting the patient to a hospital so that nursing can administer medications. The same medication regimen, as outlined earlier, can be used. Topical antibiotics should be continued for at least 1 week following clinical resolution (i.e., clear bleb fluid and absence of anterior chamber reaction).

As the clinical picture improves (decreased or absent anterior chamber inflammation, improvement in conjunctival hyperemia, or improvement in turbidity of bleb fluid), a decrease in frequency can be considered. Antibiotics should not be tapered below four times daily dosing unless FDA approved for less frequent dosing, as this can encourage drug-resistant strains of bacteria. The patients should be monitored daily until resolution of the anterior chamber inflammation has occurred.

Use of topical corticosteroids in an attempt to preserve bleb function is controversial and should be considered only after the anterior chamber is free of cells and the bleb fluid is clear. If the clinician opts to use topical corticosteroids, then Q3–6 h frequency can be considered.

Summary for the Clinician

- Blebitis is a severe, potentially vision-threatening infection that should be treated aggressively.
- Topical fourth-generation flouroquinolones or fortified cefazolin 5 % (or vancomycin 2.5 %) and tobramycin 1.5 % initially should be administered hourly around the clock.
- Hospital admission should be considered if a patient seems unable to self-administer drops at this frequency or cannot present for frequent follow-up.
- As signs improve, the topical antibiotic frequency can be decreased.

61.4 When Should I Move on to Intravitreal Injections?

If white blood cells are present in the vitreous, then it is no longer blebitis, but rather endophthalmitis. In these cases, intravitreal delivery of antibiotics is necessary. We recommend the clinical management to be in conjunction with a retina specialist, if possible. Generally, vancomycin (or clindamycin if the patient has a history of vancomycin allergy) and amikacin or ceftazidime may be considered for intravitreal delivery. In some centers, anterior chamber cell greater than 1 or 2+ is also treated with intravitreal injections, especially if the patient is pseudophakic.

Bleb-associated endophthalmitis is generally associated with *Streptococcus* species and *Haemophilus influenzae*. These organisms are typically more virulent than those seen with delayed onset endophthalmitis following cataract surgery. Therefore, pars plana vitrectomy may be considered at an earlier stage than recommended by the Endophthalmitis Vitrectomy Study [12].

Summary for the Clinician

- Vitreous white blood cells in the setting of a blebitis is considered an endophthalmitis and immediate intravitreal injection of antibiotics should be planned.
- Bleb-associated endophthalmitis is usually caused by very virulent organisms and thus a pars plana vitrectomy may be warranted before vision falls to light perception.
- Vancomycin or clindamycin and amikacin or ceftazidime are common antibiotics used for intravitreal injection in bleb-associated endophthalmitis.

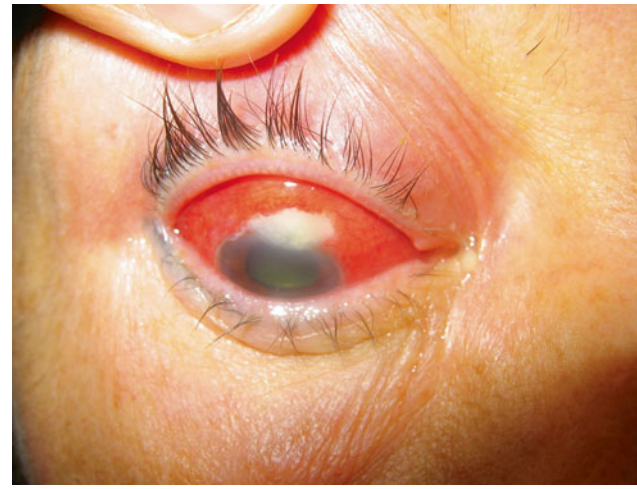

Fig. 61.1 Blebitis in an eye that is 3 years status post-mitomycin-C trabeculectomy. Eye is severely injected and bleb is purulent (Courtesy of Dr. Sumit Shah)

61.5 How Do I Manage a Patient After the Blebitis Is Resolved?

After the blebitis is resolved, the patient's glaucoma control must be considered. In some cases, inflammation induced by the infection can scar the bleb leading to IOP elevation. If the IOP is not controlled, further interventional management may be required. If a bleb leak led to blebitis and continues to leak following resolution of the infection, a bleb revision should be planned. If IOP control is lost after an episode of blebitis, medical therapy can be escalated to regain control. If medical therapy is inadequate or not tolerated, then a trabeculectomy revision, second trabeculectomy, or glaucoma drainage device procedure can be considered. It is probably best to allow a few months to pass so that inflammation settles down (Fig. 61.1).

Summary for the Clinician

- If a bleb leak led to blebitis and continues to leak, it should be repaired.
- If IOP rises after resolved blebitis, medical hypotensive therapy can be reinstituted; if medical therapy is inadequate, surgery can be planned but inflammation should be allowed to subside.

61.6 How Do I Manage Endophthalmitis in the Setting of an Exposed Tube Shunt?

If endophthalmitis occurs in the setting of an exposed tube shunt, the patient can be managed as stated in Sect. 61.4 with delivery of intravitreal antibiotics. Eroded conjunctiva may be repaired with methods such as conjunctival autografting, pedicle flaps, or additional patch grafting. Successful repair may also require relocation of the tube to a more posterior insertion or placement in a quadrant different from the original one [6]. Recommendations for removal of the glaucoma shunt device at the time of treatment in an eye with endophthalmitis remain controversial. Some advocate shunt

removal at the time of treatment because of concerns the shunt might serve as a nidus for infection [3, 13]. In contrast, others have reported successful outcomes with intravitreal antibiotics alone [14, 15]. One report indicated no difference in final visual acuity relating to whether the tube shunt was or was not removed at the time of treatment [4]. However, an extruded tube or plate causing discomfort to the patient usually requires prompt removal.

Summary for the Clinician

- Endophthalmitis in the setting of an exposed tube shunt should be managed with antibiotic therapy and repair of the exposed tube.
- Recommendations for removal of the tube shunt remains unclear; however, some advocate removal due to concerns of incomplete sterility.

References

1. Wilensky J. Late bleb leaks. In: Shaarawy TM et al., editors. Glaucoma volume 2: surgical management. London: Elselvier; 2009. p. 243–6.
2. Soltau JB, Rothman RF, Budenz DL, Greenfield DS, Feuer W, Liebmann JM, Ritch R. Risk factors for glaucoma filtering bleb infections. Arch Ophthalmol. 2000;118:338–42.
3. Gedde SJ, Scott IU, Tabandeh H, et al. Late endophthalmitis associated with glaucoma drainage implants. Ophthalmology. 2001;108:1323–7.
4. Al-Torbak AA, Al-Shahwan S, Al-Jadaan I, Al-Hommadi A, Edward DP. Endophthalmitis associated with the Ahmed glaucoma valve implant. Br J Ophthalmol. 2005;89(4):454–8.
5. Morad Y, Donaldson CE, Kim YM, et al. The Ahmed drainage implant in the treatment of pediatric glaucoma. Am J Ophthalmol. 2003;135:821–9.
6. Catoira-Boyle YPM, et al. Postoperative complications. In: Shaarawy TM, editor. Glaucoma volume 2: surgical management. London: Elselvier; 2009. p. 453–66.
7. Rhee DJ, Colby KA, Rapuano CJ, Sobrin L. Ophthalmic drug guide. New York: Springer; 2007.
8. Herbert EN, Pearce IA, McGalliard J, Wong D, Groenewald C. Vitreous penetration of levofloxacin in the uninflamed phakic human eye. Br J Ophthalmol. 2002;86:387–9.
9. Hariprasad SM, Mieler WF, Holz ER. Vitreous penetration of orally administered gatifloxacin in humans. Trans Am Ophthalmol Soc. 2002;100:153–9.
10. Hariprasad SM, Mieler WF, Holz ER. Vitreous and aqueous penetration of orally administered gatifloxacin in humans. Arch Ophthalmol. 2003;121:345–50.
11. Fiscella RG, Nguyen TKP, Cwik MJ, Phillpotts BA, Friedlander SM, Alter DC, Shapiro MJ, Blair NP, Geiser JP. Aqueous and vitreous penetration of levofloxacin after oral administration. Ophthalmology. 1999;106:2286–90.
12. Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of bacterial endophthalmitis. Arch Ophthalmol. 1995;113:1479–96.
13. Perkins TW. Endophthalmitis after placement of a Molteno implant. Ophthalmic Surg. 1990;21:733–4.
14. Krebs DB, Liebmann JM, Ritch R, et al. Late infectious endophthalmitis from exposed glaucoma setons [case report]. Arch Ophthalmol. 1992;110:174–5.
15. Ellis BD, Varley GA, Kalenak JW, et al. Bacterial endophthalmitis following cataract surgery in an eye with a preexisting Molteno implant. Ophthalmic Surg. 1993;24:117–8.

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