Pathogenesis of glaucoma

The factors that determine the development of retinal/optic nerve damage and loss of visual function have not been fully identified. While the intraocular pressure (IOP) level is the major risk factor, other issues such as the tolerance of retinal ganglion cells (RGCs) in the individual patient, the role of the supporting connective tissue at the lamina cribrosa, autoregulation of local blood supply, and perfusion pressure are likely to play a part. This chapter reviews IOP as the major factor in the pathogenesis of glaucoma with a brief overview of ocular blood flow and perfusion pressure.

Determinants of intraocular pressure

As discussed in Chapter 1, glaucoma is usually, although not invariably, associated with IOP elevation. Three factors that determine IOP are:

1. the rate of aqueous humor production by the ciliary body;
2. resistance to aqueous humor outflow across the trabecular meshwork-Schlemm's canal system (the juxtacanalicular meshwork is generally thought to be the site of greatest resistance); and
3. the level of episcleral venous pressure.

IOP elevation is generally due to increased aqueous outflow resistance, as discussed below.

Aqueous humor production and outflow in the healthy eye

Aqueous humor production

Aqueous humor is produced by the ciliary body and fills the anterior chamber (the space between the cornea and the iris) and posterior chamber (the space between the iris and lens) (Figures 2.1, 2.2) [1].

Each of the approximately 80 ciliary processes comprises a double layer of epithelium (the outer layer is pigmented, the inner layer is not) over a core of stroma and a rich supply of fenestrated capillaries. These capillaries are supplied mainly by branches of the major arterial circle of the iris [1]. The apical surfaces of the outer and inner layers of the epithelium are joined by tight junctions, which are a fundamental part of the blood–aqueous barrier [1]. The inner epithelial layer protrudes into the posterior chamber and comprises of cells containing numerous mitochondria and microvilli; these cells are thought to be the site of aqueous humor production [1].

The formation of aqueous humor and its secretion across the large surface area of the ciliary processes into the posterior chamber occurs as a result of active secretion, ultrafiltration and simple diffusion. Active secretion requires energy (hydrolysis of adenosine triphosphate) to

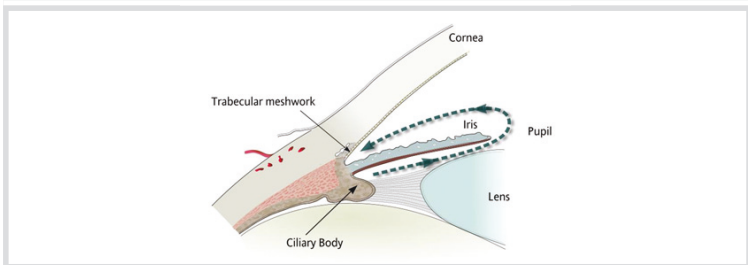**Diagrammatic section of the anterior chamber angle and ciliary body**

Figure 2.1 Diagrammatic section of the anterior chamber angle and ciliary body. Dotted line shows the normal path of aqueous humor, which is actively produced in the epithelium of the ciliary body, passes through the posterior chamber between lens and iris, into the anterior chamber to exit the eye passively via the trabecular meshwork to Schlemm's canal and into the venous system. A small proportion of aqueous in the human eye also exits through the root of the iris and the ciliary muscle, into the suprachoroidal space (uveoscleral outflow). Courtesy of Alan Lacey, reproduced with permission from © Moorfields Eye Hospital, 2013. All Rights Reserved.

Cross section of the anterior segment of the normal eye, showing sites of normal aqueous outflow
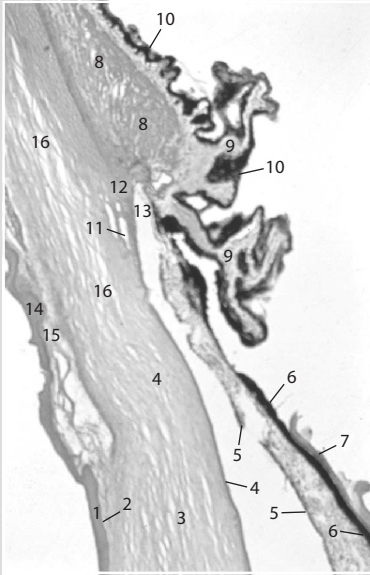
1. Epithelium of cornea
2. Bowman's layer of cornea
3. Substantia propria of cornea
4. Endothelium of cornea bordering the anterior chamber
5. Anterior border of iris
6. Posterior epithelium of iris
7. Fragment of lens attached to the iris
8. Ciliary body, pars plana
9. Ciliary processes (pars plicata)
10. Pigmented epithelium of the blind retina
11. Schlemm's canal
12. Pectinate ligament of iris (uveal trabecula)
13. Iridocorneal (drainage) angle
14. Conjunctiva
15. Episcleral tissue
16. Sclera

Figure 2.2 Cross section of the anterior segment of the normal eye, showing sites of normal aqueous outflow. Reproduced with permission from Csillag [1].

secrete substances against a concentration gradient. Active secretion is independent of pressure and accounts for the majority of aqueous production. Ultrafiltration is a pressure-dependent movement along a pressure gradient: in the ciliary processes, hydrostatic pressure differences between the capillary pressure and IOP favors movement of fluid into the eye; the oncotic gradient between the capillary and IOPs does not favor fluid movement. Diffusion is a passive process in which ions move across a membrane, according to charge and concentration.

Aqueous humor provides oxygen and nutrients to ocular tissues, and maintains the pressure and shape of the eye. Components of aqueous humor include a protein concentration around 1% of the level of plasma, antioxidants, such as ascorbate and glutathione, and certain cytokines, such as transforming growth factor-beta.

Aqueous humor is secreted into the posterior chamber from when it flows slowly through the pupil into the anterior chamber. The average rate of production of aqueous humor is 2.0–2.5 µL per minute, and the turnover rate for aqueous volume is approximately 1% per minute [2].

Aqueous humor outflow

There are two pathways for outflow of aqueous humor:

- the trabecular or conventional outflow pathway, through which most of the aqueous humor leaves the eye (this is pressure dependent [dependent on IOP]); and
- uveoscleral pathway (this is pressure independent).

Trabecular outflow pathway

Most of the aqueous humor leaves the eye by passing through the trabecular meshwork into a circular collector channel, Schlemm's canal, which is located at the corneoscleral junction and empties into aqueous veins in the scleral surface through a plexus of collector channels.

The trabecular meshwork comprises multiple layers. Each layer is composed of a collagenous connective tissue core covered by a continuous endothelial layer. Aqueous humor outflow via the trabecular meshwork is pressure-dependent and acts as a one-way valve, so that there is bulk flow of aqueous humor out of the eye but limited retrograde flow. Conventional outflow is passive. The point of maximum resistance to outflow is the juxtacanalicular trabecular meshwork (ie, the portion of trabecular meshwork closest to Schlemm's canal) and the inner wall of the canal itself.

The number of trabecular cells decreases with age, and the basement membrane thickens. In some eyes, the trabecular cells contain many pigment granules in the cytoplasm, thus giving the meshwork a brown appearance. Schlemm's canal is a single channel (average diameter of approximately 370 µm) that is traversed by tubules. The canal is connected to episcleral veins via a complex system of vessels. The episcleral veins drain into the anterior ciliary and superior ophthalmic veins, and these vessels drain into the cavernous sinus. Low IOP may be associated with collapse of the trabecular meshwork or blood reflux into Schlemm's canal.

Although blood may reflux into Schlemm's canal when the IOP is low, or episcleral venous pressure is high, the unidirectional nature of flow through trabecular meshwork prevents reflux into the anterior chamber [3].

Uveoscleral outflow pathway

Some aqueous humor exits through the root of the iris and the ciliary muscle into the suprachoroidal space. Low pressure in the suprachoroidal space provides a pressure gradient from the anterior chamber to this space, encouraging aqueous diffusion. Aqueous in the suprachoroidal space is absorbed through sclera into the connective tissue of the orbit, where it drains into blood vessels; some aqueous humor is directly absorbed by the blood vessels of the choroid.

This uveoscleral pathway provides an alternative route of aqueous absorption that can be modified pharmacologically to some degree (Figure 2.3). Although uveoscleral outflow follows a pressure gradient, it is largely pressure-independent, and is thought to comprise up to 15% of total aqueous humor outflow in humans, although this percentage varies greatly in other animals. Uveoscleral outflow is influenced by age and is increased by cycloplegia (ie, paralysis of the ciliary muscle of the eye), adrenergic agents, prostaglandin analogues and certain complications of surgery. It is decreased by miotics.

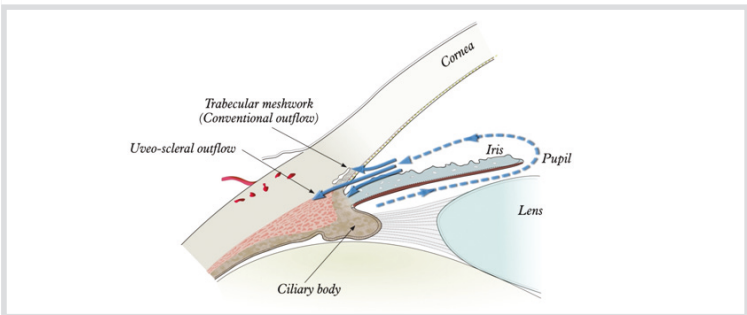**Outflow of aqueous humor through the uveoscleral pathway**

Figure 2.3 Outflow of aqueous humor through the uveoscleral pathway. Cross-section showing the normal flow of aqueous humor, but also illustrating both conventional outflow through the trabecular meshwork and uveoscleral outflow, which takes place via the root of the iris, ciliary body and suprachoroidal space. Courtesy of Alan Lacey, reproduced with permission from © Moorfields Eye Hospital, 2013. All Rights Reserved.

Disturbances in aqueous humor production and outflow

Aqueous humor is produced and circulates constantly, although there is a large variation between daytime (2–3 µl/min) [2] and nocturnal production, with the lowest levels occurring during sleep (approximately 1.4 µl/min) [4]. Various other factors influence the rate of aqueous humor production. These include:

- age;
- integrity of the blood–aqueous barrier;
- blood flow to the ciliary body (eg, reduced in carotid-occlusive disease);
- neurohormonal regulation of vascular tissue and the ciliary epithelium;
- detachment of the ciliary body (eg, after trauma);
- cyclitis or cyclitic membranes (eg, in intraocular inflammation);
- cyclophotocoagulation (eg, with the diode laser); and
- certain drugs (eg, general anesthetics, some systemic hypotensive agents).

The ratio of trabecular to uveoscleral outflow is affected by age and ocular health. Aqueous humor outflow facility varies greatly in healthy eyes and is affected by:

- age (although conflicting results have been found in cadaveric and in vivo studies, the former showing a reduction with increasing age, the latter showing no effect);
- trabecular cell function (influenced by corticosteroids) and ciliary muscle tone (influenced by cholinergic drugs);
- trauma;
- surgery (penetrating keratoplasty and aphakia may result in distortion of the trabecular meshwork spaces, influencing outflow facility);
- extracellular matrix in the trabecular meshwork (affected by corticosteroids and aging);
- trabecular meshwork damage from prolonged or severe IOP elevation; and
- angle occlusion (eg, primary angle-closure glaucoma [PACG] or neovascularization).

Impact of aqueous flow on intraocular pressure

The IOP is determined by the modified Goldmann equation (see Table 2.1), which relates the various components of inflow and outflow. It can be seen by this equation that a balance between the production (aqueous flow) and outflow determines the IOP (Table 2.2). Although aqueous flow declines with age [1], the influence of age on IOP has been less clear. Cross-sectional studies have not shown a consistent trend. One recent longitudinal study followed 339 individuals in Northern Sweden for 21 years and reported a small but significant increase in IOP of 0.05 mmHg per year in IOP [5]. An increase in outflow resistance with age has an important influence on IOP stability. The impact on IOP of a small change in aqueous flow will have a large effect on IOP if the facility of outflow is low (high outflow resistance), but less so if the facility of outflow is large (eg, as in the case of young, healthy individuals). The most common cause of IOP elevation in eyes with open angles is inadequate drainage (ie, reduced outflow) of aqueous humor due to increased resistance in the trabecular meshwork.

Modified Goldmann equation	
Equation	**Components**
$IOP=(Fa-Fu)/C+Pev$	IOP, intraocular pressure
	Fa, aqueous flow
	Fu, uveoscleral outflow
	C, facility of outflow
	Pev, episcleral venous pressure

Table 2.1 Modified Goldmann equation. As IOP can be directly measured and uveoscleral outflow cannot, this equation is usually used to calculate the latter.

Production and outflow of aqueous humor and intraocular pressure		
Outflow facility	**Change in aqueous flow**	**Change in IOP**
High outflow (eg, in young healthy individuals)	Small increase	Small increase
Low outflow (eg, in glaucoma sufferers)	Small increase	Disproportionate increase

Table 2.2 Production and outflow of aqueous humor and intraocular pressure. A small change in aqueous flow can produce a larger change in pressure, depending on facility of outflow. IOP, intraocular pressure.

Mechanisms of intraocular pressure disturbance in glaucoma
Primary open-angle glaucoma
The anterior chamber angle, by definition, is normal in primary open-angle glaucoma (POAG) and there is no evidence of iridotrabecular contact (Figure 2.4) [3]. The reduced outflow of aqueous humor in POAG is caused by reduction in the function of the trabecular meshwork, raising IOP.

Angle closure glaucoma
In angle-closure glaucoma, aqueous does not reach the trabecular meshwork because access to the anterior chamber angle is obstructed by the iris (in primary angle-closure) or sometimes other tissues (some secondary glaucomas), leading to elevated IOP levels (Figure 2.5). Angle closure is deemed to have occurred when the iris is in contact with the trabecular meshwork over part or the entire circumference of the anterior chamber angle. Angle closure may be due to intermittent apposition and, therefore, may be reversible (appositional), although prolonged iridotrabecular contact results in adhesions (synechia), and irreversible angle closure.

Angle closure may occur as a result of several possible mechanisms, both primary and secondary. Primary angle-closure is defined as

Diagram of open-angle glaucoma

Elevated resistance to outflow at the level of the trabecular meshwork

Cornea
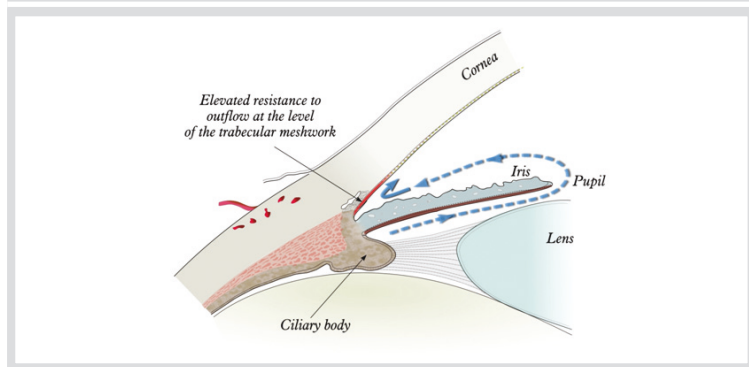
Iris

Pupil

Lens

Ciliary body

Figure 2.4 Diagram of open-angle glaucoma. When the intraocular pressure is elevated in primary open-angle glaucoma, the iridocorneal angle is anatomically open, but aqueous humor fails to drain through the trabecular meshwork to Schlemm's canal at a sufficient rate. Evidence suggests that facility of outflow reduces with age (ie, that trabecular meshwork resistance increases). The point of maximum resistance seems to be around the juxtacanalicular trabecular meshwork. Courtesy of Alan Lacey, reproduced with permission from © Moorfields Eye Hospital, 2013. All Rights Reserved.

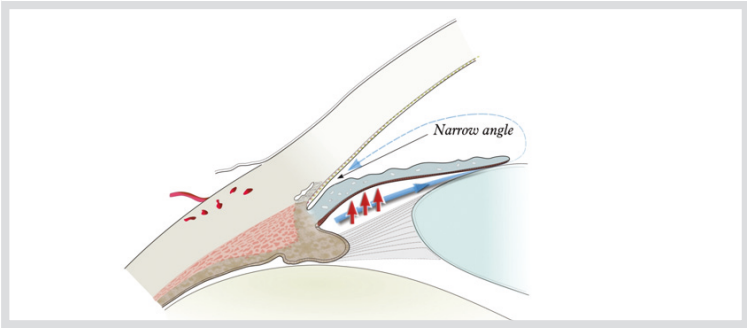**Diagram of angle-closure glaucoma (pupillary block)**

Narrow angle

Figure 2.5 Diagram of angle-closure glaucoma (pupillary block). Diagrammatic representation of angle closure secondary to pupillary block. As a result of elevated resistance to aqueous flow between the front of the lens and the pupillary margin, aqueous pressure behind the mid-periphery of the iris exceeds that in front, the iris balloons forward (arrows) and obstructs the trabecular meshwork, further presenting aqueous outflow. Courtesy of Alan Lacey, reproduced with permission from © Moorfields Eye Hospital, 2013. All Rights Reserved.

iridotrabecular apposition with or without IOP elevation or peripheral anterior synechia. PACG is diagnosed only in the presence of concurrent glaucomatous optic neuropathy (GON) in addition to iridotrabecular apposition. In cases where the optic nerve cannot be visualized, the diagnosis of PACG can be made in the presence of a closed angle if the IOP is above the 99.5% for the normal population (around 27 mmHg) [6].

The most common mechanism of primary angle-closure is pupillary block (Figures 2.5, 2.6), in which a relative obstruction to flow occurs as aqueous passes from the posterior to anterior chamber. Pupillary block usually develops in eyes that are predisposed in that they are anatomically small and hypermetropic with some constitutional narrowing of the drainage angle. Often, with increasing age, an increase in the anteroposterior thickness of the crystalline lens induces pupillary block in an eye that already has a slightly narrow angle.

Pupillary block develops when the anterior lens surface comes into contact with the pupil margin thereby obstructing the forward passage of aqueous humor from the posterior to the anterior chambers (Figure 2.5). This resultant pressure differential causes the mid-section of the iris to "balloon" forward (iris bombé), occluding the trabecular meshwork, further obstructing aqueous outflow and elevating the pressure

dramatically (Figures 2.6A, 2.6B). In primary angle-closure, the pupillary block is usually not complete and is termed *relative* pupillary block, in contradistinction to *absolute* pupillary block that sometimes occurs in secondary glaucomas, such as uveitis (see Figure 1.7).

In a proportion of eyes with primary angle-closure, an anatomical variation in the ciliary body and peripheral iris profile causes angle closure. In plateau iris, the ciliary processes are positioned more anteriorly than normal, resulting in an angulation or "roll" in the peripheral iris (Figure 2.6C). In other cases of nonpupillary block angle closure, the

Angle closure from pupillary block on anterior segment optical coherence tomography

Figure 2.6A Angle closure from pupillary block on anterior segment optical coherence tomography. Note the convexity of the peripheral iris, which is the hallmark of pupillary block. Compare this with the flat iris plane in Figure 2.6B below. Reproduced with permission from © Moorfields Eye Hospital, 2013. All Rights Reserved.

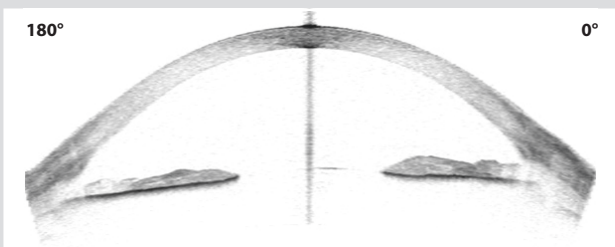### Normal angle on anterior segment optical coherence tomography for comparison

Figure 2.6B Normal angle on anterior segment optical coherence tomography for comparison. Reproduced with permission from © Moorfields Eye Hospital, 2013. All Rights Reserved.

iris root is inserted in the anterior face of the ciliary body. On pupillary dilation, either at night or pharmacologically, the peripheral iris obstructs the trabecular meshwork. While ultrasound biomicroscopy is necessary to differentiate these two variants, functionally they cause angle closure by the same mechanism.

Typically, they cause angle closure without pupillary block; however, with modern imaging techniques, an element of pupillary block is often also detected. Laser iridotomy is often performed to exclude pupillary block and make the diagnosis of plateau iris, but will often not prevent recurrent angle closure.

In chronic primary angle-closure (CPAC), chronic iridotrabecular contact results in permanent iridotrabecular adhesions, chronic IOP elevation and eventually GON. At this time CPAC becomes chronic primary angle-closure glaucoma (CPACG).

Secondary glaucoma

In secondary glaucoma, drainage is impaired as a result of trabecular meshwork obstruction (eg, secondary angle closure in neovascular glaucoma), direct trauma to the iridocorneal angle (traumatic glaucoma) or reduced trabecular meshwork function (eg, secondary open-angle glaucoma following chronic corticosteroid usage). Certain conditions, such as uveitis, may cause IOP elevation via a mixture of these mechanisms.

A narrow angle in an eye without pupillary block

Figure 2.6C A narrow angle in an eye without pupillary block. In this high-resolution optical coherence tomography example the root of the iris can be seen originating from the anterior face of the ciliary body, creating a prominent bulge in the peripheral iris, which is consequently thicker than the mid-periphery, potentially occluding the angle when the pupil dilates. In a proportion of such cases ultrasound biomicroscopy would show loss of the iridociliary sulcus, the hallmark of plateau iris syndrome. Reproduced with permission from © Moorfields Eye Hospital, 2013. All Rights Reserved.

Impact of elevated intraocular pressure on the eye

Elevated IOP adversely influences the health of intraocular tissues in a number of ways:

- Mechanical damage to the optic nerve as it passes through the lamina cribrosa:
  - The structural integrity of the lamina cribrosa is believed to be important for the long-term health of the RGC axons passing out of the eye at this, the weakest point, in the scleral wall of the eye. Laminar distortion at the optic disc may disrupt both orthograde and retrograde axoplasmic flow. This in turn reduces the integrity and ultimately the health of the RGC.
  - Direct pressure on RGC axons may also be important in eyes with very high pressure.
- Elevated IOP also reduces ocular perfusion, compromises RGC nutrition and impedes axonal transport within RGC axons.

If IOP is sufficiently elevated, it may also damage other tissues within the eye. For example, glaucoma has been implicated in retinal vein occlusion, and protracted high IOP elevation also results in increased corneal endothelial cell loss and lens opacification.

All currently available drugs for treating glaucoma act by lowering the IOP via one or both of the following mechanisms:

- reduce the production of aqueous humor; and/or
- increase the outflow of aqueous humor through the trabecular meshwork and/or the uveoscleral pathway.

Medical management of glaucoma is discussed in more detail in Chapter 4.

Variations in intraocular pressure

IOP varies between individuals and rises gradually with age, even in healthy eyes, because of aging of the trabecular meshwork. It also varies diurnally, as discussed below and in Chapter 3.

Because IOP elevation is the most important modifiable risk factor for glaucoma, accurate measurement of IOP by tonometry is paramount in diagnosing and monitoring the progression of glaucoma. Tonometry is discussed in more detail in Chapter 3.

Intraocular pressure threshold for glaucoma

A number of studies, such as the Advanced Glaucoma Intervention Study, have helped characterize the relationship between deterioration of visual field and IOP. Although, there seems to be no *fixed* IOP threshold above which glaucoma develops, an arbitrary divide between normal and high IOP has been defined as 21 mmHg because this represents two standard deviations above the mean IOP in an adult Caucasian population (see Figure 1.8). This was based on a clinical assumption that glaucomatous damage occurred only when IOP was raised, as normal tension glaucoma (NTG) was not recognized at that time. It is now clear that screening for glaucoma based solely on IOP >21 mmHg would fail to identify almost half of the individuals with glaucoma, so this criterion is no longer used to determine who needs therapy. The current consensus is that there is no clear IOP level below which pressure can be considered normal or safe, although the risk of progression seems to be very low over in individuals whose pressure is consistently in the lower part of the normal range [7].

Although several other risk factors may affect an individual's susceptibility to glaucomatous damage, IOP is currently the only one that can be effectively modified. The use of IOP targets in monitoring glaucoma management is discussed in Chapter 4.

Circadian fluctuations in intraocular pressure

IOP fluctuates over a 24-hour period (circadian fluctuation) as well as during the day (diurnal fluctuation). Circadian fluctuation in healthy eyes is less (usually 2–6 mmHg) than in eyes with glaucoma, and it has been suggested in the past that fluctuation greater than 10 mmHg is indicative of glaucoma. IOP levels can vary enormously during the day and night, and are influenced by many factors including:

- time of day;
- heartbeat;
- respiration;
- exercise;
- fluid intake;
- systemic and topical medications;

- position (recumbent or upright); and
- activities, such as diving, playing wind instruments.

In a study of 64 patients with POAG who measured their own IOP 5 times daily for 5 days using home tonometry, the range of fluctuation in IOP in one day and over multiple days were both significant independent risk factors for progression of glaucoma [8]. The nature and extent of the fluctuation, including the time at which peak IOP occur, vary between individuals; however, many individuals reach peak daytime pressures in the early morning hours while they are still in bed [9]. In this study, IOP fluctuation outside office hours was a significant risk factor for progression independent of IOP measured in the office. The study led to the concept that IOP fluctuation might be a risk factor for progression, independent of the level of IOP; however, in one study that seemed to support this hypothesis, fluctuation was not independent of mean IOP and, therefore, was not an independent risk factor [10]. In another study–a population-based randomized clinical trial of therapy for glaucoma–there was no correlation between fluctuation and progression [11].

The current consensus is that a single measurement of IOP is insufficient to identify peak IOP or mean diurnal pressure. Measurement at more than one time of day may be required if patients appear to be progressing when the IOP appears satisfactory during routine office examination. This is discussed in more detail in Chapter 3.

Ocular blood flow and glaucoma

The role of ocular, or optic nerve, blood flow in the pathogenesis of glaucoma is unclear. Given that a significant proportion of patients have NTG, and that progression of glaucoma is, not uncommonly, characterized by hemorrhages in the retinal nerve fiber layer around the optic disc [12], it seems likely that factors other than raised IOP contribute to glaucomatous optic nerve damage. For over 100 years ischemia has been thought to be one such factor; however, the exact role of vascular changes in optic nerve head disease remains unclear.

Ocular blood flow depends on both perfusion pressure (blood pressure minus IOP) and resistance to flow within the arterioles and capillary bed. A number of epidemiological studies have shown that low diastolic blood

pressure and low diastolic ocular perfusion pressure (DOPP) are associated with an increased prevalence of POAG; for example, a DOPP of less than 30 mmHg has been reported to be associated with a sixfold increase in risk of POAG [13]. The average DOPP was 53 mmHg for subjects with POAG compared with 63 mmHg for those without in the Barbados Eye Study [14]. Low ocular perfusion pressure has also been associated with increased progression of glaucoma [15]. An area of concern has been low nocturnal systemic blood pressure, or *nocturnal dipping*, in systemic blood pressure [15]. This is believed to be an issue particularly in patients with systemic hypertension who are treated aggressively.

A number of techniques exist to measure ocular blood flow (Table 2.3) [16]. These have demonstrated reduced flow in patients with glaucoma.

Methods of measuring ocular blood flow		
Technique	Measurement made	Notes
Scanning laser ophthalmoscopic angiography	With fluorescein, to measure arteriovenous passage time; with indocyanine green dye, to measure speed of blood flow entering the choroid	Superior to photographic angiography because the laser beam gives better penetration of the lens and cornea. Indocyanine green dye uses near infrared light, which penetrates retinal layers better than shorter wavelengths used with fluorescein
Confocal scanning laser Doppler flowmetry	Combines a flow meter to measure speed of blood and confocal scanning laser tomography taking images of the optic nerve head and retina	Reproducibility over time is limited
Ocular pulse measurement	Calculates flow from pulsation in the IOP during the cardiac cycle	Affected by sclera rigidity, ocular volume, heart rate, systemic blood pressure and IOP, limiting its usefulness for comparison between individuals, but not for following blood flow in a single patient. More suitable for measuring blood flow changes in an individual (eg, in response to medication) than comparisons between individuals (eg, glaucoma versus normal). Fast and easy to use, relatively inexpensive
Color Doppler ultrasound imaging	Grayscale image of anatomical details is combined with color representation of blood flow measured by Doppler shift	Absolute volume of flow not measured because vessel diameter is not measured

Table 2.3 **Methods of measuring ocular blood flow.** IOP, intraocular pressure. Adapted from Flammer [16].

For example, color Doppler imaging has shown increased resistance to flow in POAG [17] and NTG [18], and reduction in blood flow in the temporal neuroretinal rim, and the cup of the optic nerve head has been demonstrated by scanning laser Doppler flowmetry [19]; however, the relevance of this to clinical practice has not been determined.

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