Chapter 3

Circadian Changes in Intraocular Pressure

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Core Messages

- Intraocular pressure (IOP) follows a circadian rhythm
- While the suprachiasmatic nucleus controls these rhythms, an intrinsic oscillator may be present within the eye
- Dysregulation of 24-hour IOP may be responsible for some cases of glaucomatous optic neuropathy
- IOP is highest in the habitual positions during the nocturnal period
- Prostaglandin analogs and carbonic anhydrase inhibitors more effectively lower IOP during the nocturnal period than beta-adrenergic antagonists

3.1 Introduction

Circadian rhythms explain a variety of physiologic processes, including sleep, body temperature, hormone secretion, and cell regeneration. These rhythms maintain a periodicity of approximately 24 hours (24H) in light or dark, are relatively independent of external temperature, and can be reset by external stimuli. The patterns of a number of processes undergoing circadian rhythm have been linked to melatonin secretion, which peaks in the early morning, and body temperature, which is at its trough at 5 a.m.

Extensive clinical evidence indicates that intraocular pressure (IOP) follows a 24H pattern of peaks (in the morning) and troughs (in the evening). The sinusoidal 24H IOP curve suggests a dynamic regulation of the variables in the Goldmann equation (aqueous production, outflow facility, and episcleral venous pressure). Indeed, it has been well recognized that aqueous production follows a circadian cycle [1–3], peaking during the diurnal period and with sleep deprivation [4, 5]. The stimulus for these rhythms likely comes from the hypothalamus and the photic-sensitive suprachiasmatic nucleus (SCN). Neuroendocrine signaling molecules such as norepinephrine and dopamine may regulate these rhythms. Still, the persistence of these rhythms in patients with Horner syndrome may indicate an additional source of biochemical regulation of aqueous flow.

The importance of 24H IOP, particularly the nocturnal (sleep) values, has not yet been elucidated. Nevertheless, IOP remains the only clinically modifiable risk factor for glaucoma. Moreover, a number of patients with statistically average or low IOPs show progression of glaucomatous optic neuropathy. Twenty-four-hour IOP studies have demonstrated a distinct difference in IOP curves in glaucoma relative to normal subjects [5, 6]. These studies suggest the possibility that a dysregulation of circadian rhythms that may control 24H IOP contribute to the development and worsening of glaucomatous optic neuropathy. Further, peak values of IOP achieved during the nocturnal period may have to be lowered to optimally prevent worsening glaucoma.

3.2 Normal IOP Curve

IOP is typically determined in an office setting using Goldmann applanation tonometry (GAT). The limitations of GAT, including the underestimation of IOP in patients with thin or less rigid corneas, have long been recognized. Only recently, however, has the importance of habitual positioning on the clinical measurement of IOP been quantified [7]. GAT is measured in a seated position. However, up to one-third of the day is spent in a recumbent position. Episcleral venous pressure (EVP) rises when recumbent, though autoregulatory
mechanisms may modify IOP changes related to body position. In a study of normal patients conducted at the Hamilton Glaucoma Center, University of California, San Diego, a sustained rise in IOP was noted during the nocturnal period (an 8 h period during sleep), which was partially explained by the change in body position from seated to supine (Fig. 3.1) [5, 7]. When IOPs were measured while subjects were in a supine position throughout the 24H study, the nocturnal rise in IOP, though present, fitted within a biphasic IOP curve with two peaks within 24H.

The relationship of aqueous flow dynamics to 24H IOP remains unclear. Aqueous production is known to decrease by 50–60% at night [8]. However, IOP rises during the nocturnal period, partly due to positional changes [5, 7]. An increase in EVP may contribute to this rise [9]. However, when data is collected in a supine position over 24H, fluctuations in IOP are still present [5]. This underlying fluctuation in IOP suggests circadian control of IOP. This control is independent of ambient lighting and changes in corneal biomechanical properties [10, 11]. Animal studies also suggest that the nocturnal rise in IOP can be entrained by using light and dark stimuli [12].

One possible explanation for the 24H IOP measurements is that an IOP rise during the diurnal period is related to an increase in aqueous production, while a rise in the nocturnal period is due to a decrease in outflow facility. Yet, the biochemical basis of a circadian rhythm in normal subjects remains unclear. In a rabbit study, aqueous norepinephrine (but not plasma melatonin) concentrations were correlated to rises in IOP during the nocturnal period [13]. Central control of circadian changes in IOP, however, can be altered. Lesions in the SCN significantly blunt the nocturnal IOP rise, suggesting that the hypothalamus regulates daily fluctuations in IOP [14]. Furthermore, mice that lack the expression of circadian clock genes no longer show circadian changes in IOP [15]. Yet, while the SCN may modulate 24H IOP fluctuation, animals recover a circadian pattern of IOP several weeks after SCN lesions, which may indicate compensatory sources of circadian control.

### 3.3 Sources of Circadian Control

The primary regulator of circadian rhythms is the SCN, a paired nucleus located above the optic chiasm in the anterior hypothalamus. The SCN is entrained by photic stimuli detected by photoreceptors and transmitted as neural signals via the retinohypothalamic tract (Fig. 3.2).