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24-hour fluctuations in intraocular pressure as an independent risk factor for primary open-angle glaucoma

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Abstract

Purpose. In addition to the static observation of intraocular pressure at an arbitrary time point, the dynamic observation of intraocular pressure in the 24-hour rhythm is considered to be clinically useful in order to better assess the extent of day-night fluctuations.

Material and Methods. The literature review includes the current state of knowledge regarding the 24-hour fluctuations in intraocular pressure as an independent risk factor for primary open-angle glaucoma. The literature search was performed with PubMed.

Results. The intraocular pressure is neuronally regulated and is involved in the circadian regulation via the nucleus suprachiasmaticus; the normal fluctuation in intraocular pressure is 5 mmHg. In the context of systemic neurodegeneration in primary open-angle glaucoma, there is also a disturbance of the circadian rhythm. The fluctuations in intraocular pressure can be 10 mmHg or more and are an independent risk factor for glaucoma progression.

Conclusion. Thus, the goal of successful glaucoma therapy is not only to achieve an individual target pressure range, but also to normalise abnormal circadian intraocular pressure fluctuations.

Keywords

glaucoma, circadian rhythm, neurodegeneration, oxidative stress

Intraocular pressure (IOP) is currently a decisive clinical observable to decide when to start treating glaucoma and is one of the target variables in everyday practice to control glaucoma and the course of the disease. Even though glaucoma progression can only be controlled partially, IOP remains an important risk factor for glaucoma.

Therefore, it is vital to understand the importance of regulating intraocular pressure. Intraocular pressure is regulated by the production of aqueous humour in the ciliary body and by its drainage route via the trabecular meshwork and the uveoscleral drainage, while the transretinal drainage does not play a particularly important role under normal conditions. This interaction raises the question whether the processes are active or passive in nature and how they are regulated over a 24-hour period.

Today, we know that the ciliary body is a "multifunctional neuroendocrine gland"[1] that is regulated in an extremely complex manner. Hormones, neurotransmitters, and other messenger substances play an important role in increasing or reducing the production of aqueous humour. Moreover, the neural regulation of the ciliary body takes place via adrenergic and cholinergic nerve fibres[2] and both the autonomic nervous system[3] and the hypothalamus, as a higher-level regulatory factor and as part of the dienecephalon[4], are involved. This means that the production of aqueous humour is neuronally controlled and is largely actively secreted (80 %) via numerous ion pumps in the syncytium of the ciliary body epithelium, while 15 % occurs via ultrafiltration and 5 % via diffusion.[5]

However, the trabecular meshwork is an active structure that also plays a role. This filter can change its pore size using alpha actin and myosin and is biologically active through numerous ion pumps and receptors for hormones and neurotransmitters.[35,36] In addition, the trabecular meshwork is also neuronally regulated via adrenergic and cholinergic nerve fibres[37], neuropeptide Y[38] and the autonomic nervous system.[3]

The suprachiasmatic nucleus (SCN), which is also part of the hypothalamus, is responsible for the higher-level circadian regulation of body functions and hormonal processes.[6] The intrinsically photosensitive retinal ganglion cells seem to be responsible for the day-night rhythm of the SCN.[7] They express the photopigment melanopsin[8], are particularly sensitive to high-frequency light and are jointly responsible for the pupillary light reflex.[9] Their projections to the brain are manifold, but primarily they project to the SCN. In addition, the Circadian Locomotor Output Cycle protein Kaput genes – also known as CLOCK genes – are responsible for the organ-specific circadian rhythm, have regulatory tasks locally at the organ level and play an important role as activators of downstream elements. They are, thus, crucial for the generation of circadian rhythms. However, these peripheral clocks are controlled and synchronised by the „master clock": the SCN.[6] In the case of the ciliary body, it has been shown that both a peripheral clock and the SCN play a role in regulating its circadian rhythm.[1]

Primary open-angle glaucoma (POAG) is now considered a cerebral neurodegeneration[10,11] with extensive neuroinflammation.[12] In this respect, the neurodegenerative process can interfere with the normal functioning of the SCN altering the circadian rhythm, which, in turn, can induce a change in aqueous humour production in the ciliary body. This can lead to an uncontrolled fluctuation in intraocular pressure. On the other hand, the decline of retinal ganglion cells due to glaucoma can lead to a loss of intrinsically photosensitive retinal ganglion cells, which, in turn, translates into an impaired control of the SCN.

Clinically, it has been seen that POAG patients exhibit a disturbance in the circadian rhythm[13] which is partly responsible for the large fluctuations in intraocular pressure of ≥10 mmHg in untreated POAG patients, being the normal fluctuations in IOP of approximately 5 mmHg.[14] In addition to this, POAG patients can also present an altered intraocular pressure rhythm. While, in healthy patients, the highest intraocular pressure values typically occur at night[15], we know that POAG patients exhibit different rhythms which Hager[16] already classified into 5 types: the day type (divided into morning and afternoon type), the night type, the varying type, the flat type and the spike type.

What is the clinical significance of this?

Studies show increasing evidence that excessive 24-hour fluctuations in intraocular pressure are an independent risk factor for the progression of glaucoma.[17,18] High intraocular pressure leads to a strong barotraumatic stress on the lamina cribrosa, which can lead to a change in restructuring processes through increasing shear forces.[19,20] Animal trials have shown that acute increases in intraocular pressure alone cause a disturbance in axonal transport, changes in the cytoskeletal structure of the optic nerve[21] and damage the astrocytes.[22] On the other hand, pressure fluctuations can also lead to dysfunctions in axonal transport, whereby this can be due to both fluctuations in intraocular pressure[23] and in cerebrospinal fluid pressure.[24] Since intraocular pressure and cerebrospinal fluid pressure are directly related to each other via the translaminar pressure difference[25], the mechanical load on the lamina cribrosa can affect both. Interestingly, it has been shown that it is not an absolute increase in pressure, but a pressure gradient, i.e., a pressure fluctuation, that leads to an activation of cytochrome c oxidase, complex IV of the mitochondrial respiratory chain.[26] This is considered an indication of increased oxidative stress, which has also been demonstrated in conjunction with mitochondrial dysfunction on the optic nerve of donor eyes with glaucoma.[27]

Whether the different pressure types in POAG also play a role in the structural and functional operation of the optic nerve has not yet been sufficiently investigated.

In summary, it should be noted that, in addition to therapies aimed at obtaining a target pressure, limiting 24-hour fluctuations in intraocular pressure should also be included when planning a treatment against glaucoma. This is especially important for those glaucoma patients who clinically show

glaucoma progression despite currently having good intraocular pressure. In this case, an ambulatory daily pressure profile should be elaborated as a first step to look for increased IOP fluctuations. If no fluctuations are observed despite further glaucoma progression, an in-patient pressure profile should be elaborated in which the clinic should at least include a pressure measurement at midnight.

The more advanced the glaucoma damage, the smaller the range of fluctuations should be, as increasing stiffness of the tissues reduces tolerance to intraocular pressure fluctuations.[19] The recommendation for early glaucoma is to normalise the fluctuation range to 5 mmHg. A fluctuation of 4 mmHg is recommended for moderate glaucoma and 3 mmHg for advanced glaucoma. Clinical studies have shown that surgery is a better procedure to stabilise intraocular pressure fluctuations than a maximum local therapy with eye drops.[28] It is therefore advisable to consider glaucoma surgery early on.

It is also recommendable to additionally treat oxidative stress. There are still no standardised treatment recommendations for this, but a reduction in oxidative stress can be attained with the help of antioxidant agents.[29]

Cellular oxidative stress[30] leads to an intracellular accumulation of free radicals, which pathophysiologically result in 3 essential changes in cells:

1. Disruption of intracellular processes
2. Increased cell membrane permeability, including the mitochondria, which causes an uncontrolled intracellular influx of elements, proteins, messenger substances, etc. that destabilise intracellular homeostasis.
3. Impairment of the mitochondrial respiratory chain, which leads to a considerable reduction in the body's own cellular energy production (adenosine triphosphate (ATP)).

Based on this knowledge, it is reasonable to prescribe antioxidants such as vitamins C and E to decrease the presence of free radicals.[30] The administration of lecithin and citicoline, also known as CDP-choline, is useful to stabilise cell membranes and to build and repair them.[31] Coenzyme Q10 (CoQ10) is particularly recommended to support the respiratory chain.[32] This is an endogenous molecule produced in the liver and an essential component of mitochondrial enzyme complexes, indispensable for the provision of ATP.

Regarding the treatment of oxidative stress, it has been shown that combinations of different active ingredients in lower concentrations often achieve a better antioxidant effect than the individual active ingredients in high concentrations, which often exceed the threshold for the occurrence of side effects.

Substances that can be sensibly combined with CoQ10 are the antioxidants lipoic acid, vitamin E and vitamin C.[33] Studies have shown that, when lipoic acid is combined with CoQ10, the lipoic acid reduces ubiquinone by transferring an electron pair to ubiquinol and thereby increases the antioxidant capacity of CoQ10 in biomembranes. The experimental data demonstrated a superadditive effect of ubiquinone in combination with lipoic acid in preventing the peroxidation of biomembranes.

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