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Non-continuous measurement of intraocular pressure in laboratory animals

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ABSTRACT

Glaucoma is a leading cause of blindness, which is treatable but currently incurable. Numerous animal models therefore have both been and continue to be utilized in the study of numerous aspects of this condition. One important facet associated with the use of such models is the ability to accurately and reproducibly measure (by cannulation) or estimate (by tonometry) intraocular pressure (IOP). At this juncture there are several different approaches to IOP measurement in different experimental animal species, and the list continues to grow. We feel therefore that a review of this subject matter is timely and should prove useful to others who wish to perform similar measurements. The general principles underlying various types of tonometric and non-tonometric techniques for non-continuous determination of IOP are considered. There follows discussion of specific details as to how these techniques are applied to experimental animal species involved in the research of this disease. Specific comments regarding anesthesia, circadian rhythm, and animal handling are also included, especially in the case of rodents. Brief consideration is also given to possible future developments.

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1. Introduction

Glaucoma, a heterogeneous group of optic neuropathies that share characteristic pathognomic changes to the optic disk and visual field, is a leading cause of irreversible blindness in the world. Globally, 70 million people are affected by this condition (Quigley, 1996; Weinreb and Khaw, 2004). Although most advanced cases occur outside the developed world, in the United States, approximately 2.8 million people have been diagnosed with some form of glaucoma, and some 150,000 have lost all sight in both eyes to this disease. Figures for other advanced countries are proportionally similar.

There is no known cure for glaucoma. But many forms of the disease are associated with pathological elevation of intraocular pressure (IOP), and elevated IOP is the most important risk factor associated with progression of the disease. At present it is the only clinically treatable factor. Effectively and consistently lowering IOP will, in the majority of cases, retard the progress of the disease. As such, estimation of IOP in glaucoma and suspected glaucoma patients is an important facet of diagnosis and treatment. Much research effort has also been directed towards the study of this disease for many decades, and an ability to estimate IOP in the many animal models currently used is also crucial for study of the mechanisms of disease progression, as well as an ability to detect potential IOP modulating effects of drugs and test agents.

There are various methods for establishing a value for IOP. Ideally, it should be measured continuously by IOP telemetry, but this approach is still being developed and optimized, and thus lies beyond the scope of the present article. It is usually either directly measured non-continuously using invasive approaches involving

Abbreviations: AC, anterior chamber; ART, applanation resonance tonometry; BAB, blood-aqueous barrier; CCT, central corneal thickness; GAT, Goldmann applanation tonometry; IM, intramuscular; IOP, intraocular pressure; IP, intraperitoneal; IST, individual specific tonometer; NHP, non-human primate; OIT, optical interferometry tonometry; PBS, phosphate-buffered saline; PC, posterior chamber; POAG, primary open-angle glaucoma; TM, trabecular meshwork.

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cannulation of the eye, or else estimated non-continuously and non-invasively by tonometry. Tonometry in particular has evolved greatly over the last 150 years (Stamper, 2011) and there are now numerous different types of tonometer available, many of which have proven useful for assessment of IOP not only in human patients, but also in animal subjects for the purposes of research.

The general principles of IOP measurement by cannulation or estimation by tonometry are discussed below, followed by a consideration of their applications in specific experimental animal species, along with their advantages and shortcomings. Particular consideration is also given to the effects of anesthesia and circadian rhythm on IOP, and the impact of these issues on experimental design when planning a live animal IOP study. Types of tonometer applicable to different animal species are also presented, along with their respective advantages and shortcomings.

2. Invasive measurement of IOP

There are several methodologies for direct determination of IOP. All involve cannulation of the eye and therefore suffer from the disadvantages that they require the use of general anesthesia (which will affect IOP), and the globe must be punctured. Therefore they can only be performed infrequently, often no more than a few times per month. But cannulation methodology allows for IOP itself to be measured directly, with great precision and accuracy. The act of puncturing the globe however may lead to an inflammatory response, and possibly even breakdown of the blood-aqueous barrier (especially when utilizing such an approach in rabbits). Thus this invasive methodology has the potential to change the very parameter that is being measured. With the advent of better tonometers, invasive techniques have become less frequently utilized as they are usually not necessary. But this approach is still the only way to actually measure, rather than estimate, IOP, and in general it yields less measurement variation than tonometric techniques. As such, when high levels of accuracy and precision are required, invasive techniques are still sometimes warranted. Also, if a treatment is expected to lead to unusual corneal properties (for example, scarring, excessive thickness, or large changes in biomechanical properties), then tonometry may be less effective (although this should first be confirmed by an appropriate calibration). Specific details of each invasive method are outlined below. Later sections discuss the use of this methodology in different animal species.

2.1. Microcannulation of the globe

In an animal under general anesthesia a small gauge hypodermic needle (diameter up to 1 mm), or a glass microneedle (diameter 50–100 μm) supported on a micromanipulator, is inserted through the cornea into the anterior chamber (AC) at a point within 1–2 mm of the limbus (Davson, 1990). Care must be taken to avoid contacting the iris, anterior lens capsule, crystalline lens, or corneal endothelium (other than necessary at the point of puncture). Risk of damage to the iris may be reduced via the use of topical mydriatics, although this may influence IOP (Qian et al., 2012; Atalay et al., 2015).

Alternatively, the needle may be passed through the sclera a few mm posterior to the limbus, and the pars plicata of the ciliary body, to enter the posterior chamber (PC). When performed with sufficient care, pressure in the PC is generally found to be marginally higher than that of the AC (consistent with the flow of aqueous from the PC to the AC, via the pupillary margin, which rests against the lens and offers a small amount of resistance to aqueous flow) (Moses and Hart, 1987).

As another alternative, the needle may be inserted through the equatorial sclera into the vitreous. It is important in intravitreal cannulation to avoid striking the posterior lens capsule, the crystalline lens itself, or the retina. In this latter case, vitreous pressure is measured, which in practice may be slightly different from pressure in the AC or PC (Davson, 1990).

In each case the needle is attached to a length of small diameter tubing (PE60 or similar), and thence to a pre-calibrated pressure transducer, or saline column. If the latter, the correlation that 13.6 mmH_2O equals 1 mmHg is utilized, and the pressure indicated on the column under steady-state conditions is assumed to be equal to IOP (Moses and Hart, 1987; Davson, 1990; Wilson et al., 1993; Oyster, 1999).

2.2. Servo-null micropipette procedure

The servo-null micropipette procedure is an electrophysiological method for measuring IOP. A glass micropipette filled with a solution of 3 M KCl with added 0.003% carboxyfluorescein (as a visible tracer), an electrical ground reference electrode (fabricated from a $AgCl_2$ pellet), and a servo-null device are utilized (Avila et al., 2001). The high concentration of KCl inside the micropipette renders its internal electrical resistance much less than that of extracellular fluid. Upon advancement of the micropipette tip through the cornea into the AC, the IOP within forces aqueous humor into its lumen, thus displacing the KCl solution towards the micropipette shank, increasing resistance at the tip. Resistance is continuously monitored, and a signal is passed to a vacuum pressure pump to increase the counter pressure against the column of advancing aqueous until the KCl solution is restored to its original position within the tip. At this point electrical resistance at the tip is now once more rendered equal to its pre-cannulation minimal value. The counter-pressure required to achieve this is equal to IOP. This method provides a very accurate and reproducible value, and offers the advantage over simple microcannulation of the AC in that the cannulating micropipette has a considerably smaller diameter (approximately 5 μm), and thus causes less trauma to the cornea. But the drawback of this method is that a dedicated servo-null apparatus is required.

3. Non-invasive (tonometric) estimate of IOP

It is possible to gain reasonably accurate and reproducible estimates of IOP non-invasively using a specialized instrument, known as a tonometer. There are many different types of tonometer currently available (for review, see Stamper, 2011). But no tonometer yet devised actually measures IOP. Rather, tonometers of any type measure various other parameters, from which IOP is then estimated. Further, no tonometer functions with perfect accuracy or precision over the entire range of IOP or eye conditions that they may encounter. In these respects, tonometry is less accurate than the cannulation methods discussed above. Nevertheless, because of its non-invasive nature, and because there is no requirement for general anesthesia (which can affect IOP) tonometry is a central facet of clinical ophthalmology, optometry, and vision science.

3.1. A brief history of tonometry

In 1863 Albrecht von Graefe devised the first instrument specifically designed to estimate IOP (Stamper, 2011). This tonometer worked on the principle of measuring the degree of scleral indentation produced by a weight-loaded plunger. Two years later Donders invented a spring-loaded scleral indentation device (Stamper, 2011). Adolph Weber in 1867 produced a tonometer that operated on the principle of applanation rather than indentation (Stamper, 2011). Subsequent developments of these instruments,

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