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Research article

Aqueous outflow regulation: Optical coherence tomography implicates pressure-dependent tissue motion

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ABSTRACT

Glaucoma is a leading cause of blindness worldwide and results from damage to the optic nerve. Currently, intraocular pressure is the only treatable risk factor. Changes in aqueous outflow regulate pressure; regulation becomes abnormal in glaucoma. From inside the eye aqueous flows out through the trabecular meshwork into a venous sinus called Schlemm's canal, next into collector channels and finally returns to the episcleral vessels of the venous system. The location of aqueous outflow regulation is unknown. *Ex vivo* and *in vivo* studies implicate both pressure-dependent trabecular tissue motion and tissues distal to Schlemm's canal in regulation of aqueous outflow. Technologies have not previously been available to study these issues. New *ex vivo* imaging in human eyes identifies hinged flaps or leaflets at collector channel entrances using a high-resolution spectral domain optical coherence tomography (SD-OCT) platform. The hinged flaps open and close in synchrony with pressure-dependent trabecular meshwork motion. The SD-OCT platform images from the trabecular meshwork surface while experimentally changing transtrabecular pressure gradients. New *in vivo* imaging in human eyes uses a motion sensitive technology, phase-sensitive OCT to quantitate real-time pulse-dependent trabecular tissue motion as well as absence of such motion when aqueous access to the outflow system is blocked. The recent studies suggest that aqueous outflow regulation results from synchronous pressure-dependent motion involving a network of interconnected tissues including those distal to Schlemm's canal. The new imaging technologies may shed light on glaucoma mechanisms and provide guidance in the management of medical, laser and surgical decisions in glaucoma.

1. Introduction

1.1. Overview

Glaucoma is a leading cause of irreversible blindness in the world and results from damage to the optic nerve (Quigley and Broman, 2006). Intraocular pressure (IOP) is the only treatable risk factor (Heijl et al., 2009). Control of IOP regulation resides within the aqueous outflow system of the eye (Grant, 1958) and IOP regulation becomes abnormal in glaucoma (Grant, 1958; Gabelt & Kaufman, 2011). This article focuses on intrinsic abnormalities of the outflow system in glaucoma in contrast to identifiable extrinsic factors. The intrinsic outflow system abnormality in glaucoma is unknown but is described as primary open angle glaucoma (POAG); the term is reflective of the lack of a clearly identified cause. The term "glaucoma" in this review article will refer only to the enigmatic disease of POAG.

1.2. Pathway of aqueous outflow

Aqueous flows from the anterior chamber through the

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trabecular meshwork (TM) into Schlemm's canal (SC) followed by passage into collector channel entrances (CCE) along SC external wall. From the CCE, aqueous-containing vessels course outward to discharge aqueous to visible episcleral and conjunctival veins on the scleral surface. Because aqueous must flow through these tissues, TM tissue configuration determines aqueous outflow and IOP regulation.

1.3. Localized regulation of aqueous outflow

A location between the TM lamellae and the lining of SC inner wall is called the juxtacanalicular space. A prevalent view is that extracellular matrix material (ECM) in the juxtacanalicular space acts like a filter to provide passive resistance to aqueous outflow. Modulation of the properties of the ECM, in conjunction with SC inner wall endothelium interactions, is thought to provide an adjustable resistance. A large body of evidence and carefully reasoned arguments favor the juxtacanalicular space as the primary site of IOP regulation (Gabelt & Kaufman, 2011; Johnstone, 2009). While ECM in the juxtacanalicular space is undoubtedly important and perhaps central to IOP control, imaging evidence suggests additional factors may be involved in controlling aqueous outflow and IOP.

1.4. Distributed regulation of aqueous outflow

A passive filter at a single location in the juxtacanalicular space may solely regulate aqueous outflow. If so, there is no need for embarking on the studies of tissue motion described in this review. Section 2 provides a diverse background of evidence pointing to the benefit of exploring features of a more complex regulatory framework. The background evidence points to the benefit of studies of TM and CCE entrance motion. Such studies can help to provide an integrated regulatory model to predict and explain *in vivo* aqueous outflow system behavior in glaucoma.

Evidence from imaging demonstrates pulsatile aqueous outflow and pulse-dependent, pressure-induced physical motion of both the TM and the CCE. *In vivo* imaging studies reveal coordinated, continuously oscillating pressure-dependent pulse waves of aqueous leaving SC (Goldmann, 1946; Ascher, 1942a) and synchronous changes of shape of the pathways through which aqueous flows (Li et al., 2013). Rather than being limited to a single site, aqueous outflow and IOP regulation may result from tensional integration involving subcellular (Johnstone, 2014), cellular (Johnstone, 1979) and tissue-level (Johnstone, 1979, 2004) prestress that permits coordinated synchronous tissue-wide responses.

1.5. Article goals

1) To review evidence for the role of distributed tissue-wide pressure-dependent motion in controlling aqueous outflow. 2) To describe a new spectral domain optical coherence (SD-OCT) technology that permits *ex vivo* high resolution imaging of hinged collagen flaps at CCE, a tissue geometry that allows the entrances to open and close. 3) To use the same SD-OCT technology to identify synchronous pressure-dependent TM and CCE motion. 4) To describe a second new imaging technology with high sensitivity to tissue motion, phase-based OCT (PhS-OCT) that permits *in vivo* imaging of pulse-dependent motion of outflow system structures.

2. Coordinated proximal and distal tissue motion

2.1. Glaucoma surgery points to distal resistance

2.1.1. SC glaucoma surgeries bypass the TM

A series of recently developed minimally invasive glaucoma surgeries (MIGS) bypass the TM providing access to the distal outflow pathways of the eye (Bahler et al., 2012; Johnstone et al., 2014). The procedures are relatively effective, typically lowering IOP to the mid teens (Kaplowitz et al., 2014); risks are modest making the procedures an attractive alternative to glaucoma filtering surgery (Pfeiffer et al., 2015; Grover et al., 2014; Neuhann, 2015). However, it may be argued that the procedures are far from effective in many patients and at times do not lower the pressure more than phacoemulsification alone. Also the procedures do not typically reduce IOP to near episcleral venous pressure (EVP) levels as might be expected if most of the outflow system resistance was in the TM (Richter and Coleman, 2016). Together these findings suggest that the relative ineffectiveness of MIGS needs to be better explained.

2.1.2. IOP levels found after SC surgery suggest distal resistance

The typical post surgery IOP that is achieved (Brandao and Grieshaber, 2013; Saheb and Ahmed, 2012) suggests that resistance distal to SC is important and is probably close to the external wall of SC (Schuman et al., 1999). Perfusion studies also find half or more of the resistance is distal to the TM (Ellingsen and Grant, 1972; Rosenquist et al., 1989). In addition, experimental microsurgery (Ellingsen and Grant, 1972; Johnstone and Grant, 1973a; Van Buskirk, 1982) and anatomic studies demonstrate many attachments between the TM (Johnstone, 1974, 2004; Rohen and Rentsch, 1968; Smit and Johnstone, 2002) and the CCE area, suggesting that control of outflow may not be limited to a single site, but rather may be a result of coordinated behavior of connected tissues.

The relative efficacy of the MIGS and yet the inability to explain residual distal outflow resistance point to the need to better understand global tissue mechanics of the outflow system (Loewen and Schuman, 2013), particularly the distal pathways. Rapidly evolving new OCT imaging technology that can image synchronous TM and CCE motion in the laboratory (Li et al., 2013) and trabecular tissue motion in humans in real time (Hariri et al., 2014; Sun et al., 2015) suggest it may be possible to gain a better understanding of intrinsic outflow control mechanisms.

2.2. Imaging of pulsatile aqueous outflow abnormalities in glaucoma

2.2.1. Pulsatile aqueous outflow into episcleral veins

Reports of the discovery of pulsatile aqueous outflow and aqueous vein identification occurred simultaneously; the pulsatile nature of aqueous outflow was a salient feature discussed in the original papers as a means of aqueous vein recognition (Goldmann, 1946; Ascher, 1942a). Pulsatile outflow originates from SC and is synchronous with the ocular pulse (Fig. 1) (Ascher, 1961; Johnstone et al., 2010). The ocular pulse in turn results from changes in choroidal volume that occur with the cardiac cycle (Phillips et al., 1992). Video imaging demonstrates pulse-dependent patterns of aqueous outflow from SC into CCE (Johnstone, 2006) (Fig. 2). Directly verifiable video imaging also provides quantitative measurements of the volume of the pulse waves of aqueous entering the aqueous veins (Stepanik, 1954).

2.2.2. Pulsatile aqueous outflow abnormalities identify glaucoma and its severity

Pulsatile outflow from SC into the aqueous veins is altered in

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