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Review Article

Retinal oximetry in glaucoma: investigations and findings reviewed

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ABSTRACT.
Abnormalities of the retinal blood supply have been widely implicated in primary open-angle glaucoma (POAG). Impaired blood supply to the retina and optic nerve head (ONH) may be a primary pathophysiologic mechanism contributing to POAG ('vascular hypothesis'). However, the decreased metabolic activity of atrophic tissue is itself known to induce both vascular changes and decreased blood flow due to reduced oxygen demand. Therefore, primary nonvascular factors could potentially induce glaucomatous atrophy, with subsequent secondary vascular pathology ('mechanical hypothesis'). Retinal oximetry holds great promise in the investigation of glaucoma pathogenesis, as it can provide useful data on retinal metabolic oxygen demand, especially when combined with measurements of retinal blood flow. This review surveys the research on retinal metabolism in POAG using spectroscopic retinal oximetry. The use of mathematical models in combination with oximetric data to investigate the role of retinal metabolism and oxygen supply in POAG is also discussed.

Key words: mathematical modelling – normal tension glaucoma – ocular blood flow – primary open-angle glaucoma – retinal oximetry – retinal oxygen demand

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Introduction

Glaucoma is a remarkably complex disease. Though it is a leading cause of irreversible blindness worldwide (Flaxman et al. 2017), our understanding of its pathogenesis, prevention and treatment remains limited. Fundamentally, glaucoma is a degenerative disease of the optic nerve and retina (Jonas et al. 2017). But rather than being a singular disease, 'glaucoma' instead identifies a diverse range of disorders of variable aetiology and uncertain pathophysiology that all ultimately converge on a common end-point of progressive retinal ganglion cell atrophy, optic neuropathy and consequent visual field loss.

The pathophysiology of the most common form of glaucoma, primary open-angle glaucoma (POAG), is particularly uncertain. Historically, the prevailing wisdom was that POAG results from chronically elevated intraocular pressure (IOP) leading to mechanically induced optic nerve damage. Indeed, IOP is presently the only conclusively established modifiable risk factor for the progression of POAG and is the target of all currently approved glaucoma therapies (Conlon et al. 2017). Yet some patients develop POAG without elevated IOP, while other patients with chronically elevated IOP fail to develop POAG (Kass et al. 2002). Therefore, despite frequently playing a central role in the disease process, elevated IOP is curiously neither a necessary nor sufficient factor in the pathogenesis of POAG. Other factors that have been strongly implicated in the development of POAG, independent of elevated IOP, include hypertension (Chung et al. 2015), hypotension (Chung et al. 2015), nocturnal blood pressure dips (Graham & Drance 1999; Melgarejo et al. 2018), decreased ocular blood flow (Flammer et al. 2002), reduced ocular perfusion pressure (Costa et al. 2014), vascular endothelial cell dysfunction (Resch et al. 2009; Li et al. 2016) and impaired vascular autoregulation (Pasquale 2016).

The diverse range of risk factors associated with the pathogenesis of POAG can be broadly classified into two categories (Fechtner & Weinreb 1994): (1) elevated IOP and (2) haemodynamic abnormalities. Consequently, two main hypotheses of POAG pathogenesis have emerged in the literature paralleling these two broad categories: a mechanical hypothesis (Fechtner & Weinreb 1994) and a vascular hypothesis (Flammer 1994), respectively. The exact role these two mechanisms play, either individually or jointly, in the

pathogenesis of POAG has not yet been fully established.

The mechanical hypothesis of POAG draws upon strong evidence that elevated IOP is directly correlated with the development and progression of glaucomatous disease (Leske et al. 2003). It theorizes that glaucomatous changes in the retina and optic nerve in patients with 'high-tension' POAG (HT-POAG) are a consequence of chronically elevated IOP exerting mechanical stress upon the retinal surface, optic nerve and lamina cribrosa (Burgoyne et al. 2005). Such stresses may induce damage to the optic nerve by a variety of factors, including disturbance of critical axoplasmic flow, alterations in nourishment of extracellular matrix at the optic nerve head (ONH) and direct compression of the vascular supply to the ONH (Fechtner & Weinreb 1994).

However, this mechanical hypothesis cannot account for the frequent development of POAG in the absence of elevated IOP – 'normal tension' glaucoma (NTG). Consequently, the vascular hypothesis suggests that impairment of the blood supply to the retina and/or ONH is largely responsible for the development of POAG (Flammer 1994). As one of the most metabolically active tissues in the human body (Wong-Riley 2010), the retina requires a constant supply of oxygen for its function. The supply of oxygen to the retina is determined by both ocular blood flow (OBF) and ocular perfusion pressure ((OPP), clinically approximated as the difference between two-thirds of the mean arterial pressure and IOP) (Schmidl et al. 2011). 'Normal tension' glaucoma (NTG) eyes have consistently been found to feature both reduced OBF and reduced OPP (Fan et al. 2015; Abegão Pinto et al. 2016). Moreover, the retina relies on vascular autoregulatory mechanisms to maintain stable retinal blood flow (RBF) – and therefore stable oxygen supply – across a range of perfusion pressures (Pournaras et al. 2008). Fluctuation between ischaemia and subsequent reperfusion due to unstable blood flow can cause reperfusion injury by inducing the release of highly cytotoxic reactive oxygen species (McMonnies 2018). Impaired vascular autoregulatory mechanisms and resultant instability in the blood supply can therefore induce oxidative stress and tissue damage in the retina (Benoist d'Azy et al. 2016). Vascular autoregulatory mechanisms have frequently been found to be impaired in both NTG (Mozaffarieh & Flammer 2013) and HT-POAG (Bata et al. 2019). Additionally, several systemic diseases involving underlying vascular insufficiency and dysregulation have been found to correlate with POAG, including diabetes (Zhou et al. 2014), migraine (Wang et al. 1997; Gramer et al. 2015), sleep apnoea (Shi et al. 2015), cerebrovascular disease (Harris et al. 2013) and neurodegenerative disease (Jindal 2013).

A strong association between POAG and abnormalities of the retinal vasculature has been well established (Chan et al. 2017). It may be that these abnormalities are the primary cause of tissue atrophy due to vascular insufficiency and decreased oxygen supply. However, it is also known that tissue atrophy itself results in decreased blood flow as regional metabolic demand for oxygen diminishes (Sebag et al. 1989). A critical question therefore arises: are vascular abnormalities in POAG eyes a primary driver of the disease process or a secondary consequence of it? The vascular hypothesis would assume the former, while the mechanical hypothesis would favour the latter. Indeed, a combination of both mechanical and vascular factors may be simultaneous or synergistic in their influence on the course of the disease, further complicating the identification of a primary mechanism for POAG.

The key to answering this question may lie in the evaluation of retinal oxygenation (Tobe et al. 2013; Yap et al. 2018). Based on the Fick principle, the arterio-venous difference in oxygen saturation (AVO_2) of a metabolically active tissue is equal to the ratio of oxygen demand to blood flow, a relationship that is true of the retina (Hickam & Frayser 1966): $AVO_2 \propto \frac{\text{metabolic oxygen demand}}{\text{RBF}}$. Examination of oxygen saturation in the retinal arterioles (SaO_2), venules (SvO_2) and the difference between them (AVO_2) can therefore give valuable insight into the role of oxygen supply and metabolism in the pathogenesis of POAG, especially when combined with concurrent measurements of RBF (Werkmeister et al. 2015). If chronic ischaemia is a primary cause of glaucomatous tissue atrophy, then either lower SaO_2 or decreased RBF might be expected in POAG eyes relative to healthy ones, indicative of a decreased oxygen supply. In healthy human retinas, the oxygen extraction has been shown to remain constant even in the context of hypoxia (Palkovits et al. 2014). Therefore, a reduced AVO_2 in POAG eyes may reflect a decrease in metabolic demand due to tissue loss, or conversely reflect a primary insult pathway in POAG. It is also important to consider that changes in RBF may result in alternations in SvO_2 and AVO_2, potentially offsetting metabolism. Retinal oximetry – the measurement of oxygen saturation in the retinal vasculature – has thus found important employment in the investigation of this question of cause and consequence.

Noninvasive retinal oximetry: a technological overview

Accurate and precise measurement of retinal oxygen levels is challenging. Invasive techniques such as oxygen-sensitive microelectrodes have been employed with success in the measurement of retinal oxygen tension in animal models (Hogeboom Van Buggenum et al. 1996; Linsenmeier & Yancey 2017; Whalen et al. 2017). However, these techniques are unsuitable for use in human subjects due to their invasive nature. Tools for noninvasive retinal oximetry are therefore necessary for practical and ethical human research, as well as clinical use.

Frayser and Hickam (1965) pioneered the use of noninvasive retinal oximetry, developing a photographic technique based on the prior observation (Hickam & Frayser 1949) that haemoglobin's absorption of specific wavelengths of light (its 'optical density', OD) depends upon its oxygen saturation. They further determined that the ratio between the OD of haemoglobin visualized with an oxygen-*sensitive* wavelength of light (e.g. red light, $\lambda = 510$ nm) versus an oxygen-*insensitive* wavelength (e.g. infrared light, $\lambda = 640$nm) is directly and linearly proportional to the haemoglobin oxygen saturation (SO_2):

$$SO_2 = \frac{[HbO_2]}{[Hb] + [HbO_2]} \propto \frac{OD_{oxygen-sensitive}}{OD_{oxygen-insensitive}} = \text{Optical Density Ratio}$$

This 'optical density ratio' (ODR) can be calculated from the brightness values in the fundus photograph (Harris et al. 2003). Early oximetric studies used photographic film, calculating SaO_2 by analysing pigment intensity in photographs produced using different wavelengths of light, while later studies have used digital photography. Since the 1950s, this basic principle has formed the bedrock of spectroscopic oximetry – oximetry by analysis of light – as it has progressed to involve digital imaging techniques (Beach et al. 1999) and automatic analysis by software algorithm (Hardarson et al. 2006). Beach (2014) provides an excellent review of the detailed history and evolution of these developments.

At present, two major instruments utilizing the 'two-wave' spectroscopic technique described above are commercially available (MacKenzie et al. 2017): Oxymap (Reykjavik, Iceland) and Imedos Vesselmap (Jena, Germany). Both systems can be installed on a conventional fundus camera and can automatically calculate retinal saturation by analysing two images captured simultaneously at different wavelengths (Rilvén et al. 2017). Both systems have been validated and shown to provide highly reproducible measurements (Geirsdottir et al. 2012; Palsson et al. 2012; Yip et al. 2014) that are sensitive to variations in retinal SO_2 (Hardarson et al. 2006; Hammer et al. 2008). These instruments have been productively employed in the investigation of various ischaemic retinal diseases (Boeckaert et al. 2012), including diabetic retinopathy, age-related macular degeneration, retinal vein occlusion, retinal artery occlusion, anterior ischaemic optic neuropathy, retinopathy of prematurity and glaucoma.

However, the two-wave spectroscopic technique has some important limitations. The direct relationship between ODR and SO_2 only holds when haemoglobin is evaluated directly, and hence, the relationship technically only holds with accuracy when applied to haemolysed blood, absent light interference from vessel walls, red blood cell membranes, retinal pigment and other structures. In clinical use, the results obtained from retinal spectroscopic oximetry are affected by interactions of the incident light with these structures (Harris et al. 2003). Therefore, to provide accurate measurements of SO_2, the technique requires careful calibration to account for such interference by normalizing the data to either the subject's own measured arterial haemoglobin saturation (Traustason et al. 2011; Palkovits et al. 2013) or expected normative values from the subject's population (MacKenzie et al. 2017). Without such calibration, measurements obtained can only be interpreted relative to other measurements from the same retina. Vessel size also influences the spectroscopic measurements and can be a source of error (Rodriguez et al. 2016), though this effect can be sufficiently mitigated by correcting for vessel calibre (Geirsdottir et al. 2012). Blood flow velocity may also influence oximetric measurements (Jeppesen & Bek 2019). Furthermore, anatomic differences between patients may play a confounding role. For example, differences in lens opacity, as in the case of cataract, have been shown to distort oximetry readings (Patel et al. 2013; Heitmar & Attardo 2016), which may limit utility in longitudinal investigations (Berkowitz et al. 2002). Ethnic variations in retinal pigmentation can also alter oximetry readings (Delori & Pflibsen 1989; Beach et al. 1999; Rodriguez et al. 2016); South Asian eyes (Cheng et al. 2016) and African eyes (Beach et al. 1999) notably tend to have higher retinal pigmentation than European eyes, possibly leading to discrepancies between data obtained from these two populations. Finally, as tissue oxygen extraction depends on both blood oxygen content and blood flow, measurement of RBF is necessary for the accurate interpretation of retinal metabolism from oximetric data. Despite these limitations, two-wave spectroscopic oximetry technology is currently the most widely used method of retinal oximetry in human subjects.

Other spectroscopic techniques have been developed in an attempt to avoid some of the limitations of dual-wave retinal oximetry. These include multispectral and hyperspectral oximetry that use multiple wavelengths of light that target various retinal structures (Gramatikov 2014; MacKenzie et al. 2017). Various modes of multispectral imaging have been validated for the measurement of SO_2 in whole blood (Mordant et al. 2011; Desjardins et al. 2016). However, the technology generally suffers from prolonged acquisition time and adds transient physiologic variations in oxygen saturation (MacKenzie et al. 2017). Recently, a 'snap-shot multispectral imaging' technique has been proposed to obviate these concerns by acquiring data from several spectral wavelengths simultaneously (Gao et al. 2011; Hendargo et al. 2015). Preliminary work has also been performed with hyperspectral oximetry in the clinical investigation of POAG (Desjardins et al. 2016; Shahidi et al. 2017). Scanning laser ophthalmoscopy has also been utilized in spectroscopic oximetry (Smith et al. 1998; Li et al. 2011; Kristjansdottir et al. 2014; Aref et al. 2019). Using lasers for image acquisition minimizes fundal light exposure, reducing light-induced variations in retinal metabolism and oxygen demand; however, there is high inter-eye and intra-eye measurement variability with this technique (Kristjansdottir et al. 2014). Spectroscopic technology has also been combined with optical coherence tomography (OCT) to produce the nascent technology of spectroscopic OCT (S-OCT). S-OCT allows retinal oxygen saturation to be mapped on three-dimensional images of the tissue, providing data on the spatial distribution of oxygen beyond what can be derived from a conventional two-dimensional image of the fundus (Kagemann et al. 2007; Lu et al. 2008). S-OCT can also be combined with retinal flow imaging (Linsenmeier & Zhang 2017), enabling simultaneous evaluation of RBF and SO_2, estimating retinal metabolic demand from AVO_2 (Aref et al. 2019). However, as with multispectral oximetry, the modality requires long acquisition times and has limited available data (Chih-Wei Lu et al. 2008; Kashani et al. 2014; Valmaggia et al. 2014; Zhang et al. 2017; Sanborn & Wroblewski 2018).

Finally, MRI with blood-oxygen-level-dependent contrast has been explored for oximetry (Duong et al. 2002) providing simultaneous structural and functional; however, it has limited evaluation in human subjects

(Ito & Berkowitz 2001; Berkowitz et al. 2002).

Retinal oxygenation in primary open-angle glaucoma

The data from retinal oximetry in POAG is currently conflicting. Data on retinal arteriolar saturation are the most consistent, largely suggesting no significant difference between retinal SaO_2 in POAG eyes compared with healthy eyes (Michelson & Scibor 2006; Ito et al. 2008; Olafsdottir et al. 2014; Ramm et al. 2014; Sehi et al., 2014a,2014b; Cheng et al. 2016; Shahidi et al. 2017). This finding is further supported by data from the Leuven Eye Study (Abegão Pinto et al. 2016), one of the largest databases of retinal oximetry data in POAG, which showed no difference in SaO_2 between normal, HT-POAG and NTG patients. Moreover, retinal SaO_2 appears not to vary with severity of visual impairment (Olafsdottir et al. 2011; Olafsdottir et al. 2014; Vandewalle et al. 2014; Cheng et al. 2016; Aref et al. 2019) or degree of structural atrophy (Michelson & Scibor 2006; Vandewalle et al. 2014) in POAG. Similarly, studies that used oximetry to compare retinal hemispheres in asymmetric POAG have found no difference in SaO_2 between hemifields of varying visual deficit (Shimazaki et al. 2016; Yap et al. 2017; Shimazaki et al. 2018). Yet, the finding of normal retinal SaO_2 in POAG is not wholly uncontested: Van Keer et al. (2015) found higher retinal SaO_2 in POAG eyes compared with healthy eyes, a finding they could not attribute to any identifiable confounding factors within their study. However, their unique findings may in part be due to differences between instruments used and difficulties with precise calibration. Overall, the weight of the current evidence strongly suggests that retinal SaO_2 is normal in POAG.

Importantly, as tissue oxygen delivery is a product of both arterial oxygen content and blood flow (Habler & Messmer 1997), this finding by no means rules out reduced oxygen delivery in POAG, which may still result from decreased RBF in the context of normal SaO2. Moreover, the cross-sectional nature of the above studies limits their ability to assess for intermittent ischaemia, which may be absent at the time of measurement. Finally, the patients in most of these studies were concurrently treated for their disease with a variety of therapies. It has been shown that POAG therapy may increase retinal SaO_2, as discussed below, making medical treatment a potential confounding factor. Longitudinal prospective and retrospective studies on untreated patients are therefore necessary to further clarify the presence and role of intermittent ischaemia in POAG pathogenesis.

The evidence regarding retinal SvO_2 in POAG is less consistent. Several studies have demonstrated that an increase in retinal SvO_2 (Mordant et al. 2014; Ramm et al. 2014; Van Keer et al. 2015; Hammer et al. 2016) and a decrease in AVO_2 (Mordant et al. 2014; Ramm et al. 2014; Van Keer et al. 2015) may be found in eyes with POAG. Further studies have correlated the magnitude of these changes with severity of glaucomatous damage and visual field loss (Michelson & Scibor 2006; Olafsdottir et al. 2011; Olafsdottir et al. 2014; Vandewalle et al. 2014; Shimazaki et al. 2016; Shahidi et al. 2017; Shimazaki et al. 2018), though this correlation has also been challenged (Mordant et al. 2014; Hammer et al. 2016; Aref et al. 2019). As AVO_2 is directly proportional to tissue metabolic oxygen demand and inversely proportional to blood flow (Hickam & Frayser 1966), decreased retinal AVO_2 in POAG may reflect either increased RBF or decreased retinal metabolism. Retinal blood flow (RBF) is frequently reduced in POAG (Hamard et al. 1994) in proportion to disease severity (Plange et al. 2006; Sehi et al., 2014a,2014b; Shimazaki et al. 2018; Aref et al. 2019). Therefore, the observed decrease in AVO_2 in POAG eyes is likely a consequence of reduced tissue metabolic demand, lending support to the hypothesis that the vascular changes observed in POAG are a consequence of primary tissue atrophy.

On the other hand, several major studies have shown no statistically significant difference in retinal SvO_2 (Michelson & Scibor 2006; Goharian et al. 2014; Olafsdottir et al. 2014; Sehi et al., 2014a,2014b; Cheng et al. 2016; Shahidi et al. 2017) or AVO_2 (Michelson & Scibor 2006; Olafsdottir et al. 2014; Sehi et al., 2014a,2014b; Cheng et al. 2016; Shahidi et al. 2017) between POAG and healthy eyes. The Leuven Eye Study showed no difference in retinal SvO_2 between HT-POAG and healthy subjects, although they do note elevated SvO_2 in NTG subjects (Abegão Pinto et al. 2016). Olafsdottir et al. (2014) and Shahidi et al. (2017) also found higher SvO_2 in advanced POAG only, but not in mild POAG. Finally, Goharian et al. (2014) found increased AVO_2 in POAG eyes compared with healthy controls. Together, these findings may be taken to challenge the hypothesis that the vascular changes observed in POAG are a consequence of tissue atrophy and reduced metabolic demand. However, as SvO_2 would be expected to decrease in the context of the decreased RBF frequently observed in POAG, normal SvO_2 in this setting may support the hypothesis of reduced metabolic demand in POAG.

It is unclear why the oximetric data on retinal SvO_2 and AVO_2 in POAG are inconsistent in their conclusions. Variations in RBF and vessel calibre across ethnicities (Wong et al. 2006; Guidoboni et al. 2013) and disease severities (Plange et al. 2006; Sehi et al., 2014a,2014b; Shimazaki et al. 2018) may play a confounding role by independently affecting AVO_2. Moreover, variations in lens opacity (Patel et al. 2013; Heitmar & Attardo 2016) and retinal pigmentation (Delori & Pflibsen 1989; Beach et al. 1999; Rodriguez et al. 2016) are known to distort oximetry readings. Most study participants were also concurrently treated for their disease, and certain POAG therapies have been shown to alter retinal SvO_2 as described below. Variable effects of medical treatments on retinal oxygen metabolism and saturation may therefore also play a role in producing conflicting data. Finally, many of the cited studies also do not clearly differentiate between subjects with HT-POAG and NTG, further complicating data interpretation. The question of retinal SvO_2 and, by extension, retinal metabolic demand in POAG therefore remains an unsettled issue.

Retinal oxygenation in normal tension glaucoma

While the above studies address POAG in general, research has also been

conducted on retinal oxygen saturation in NTG specifically. Among the early studies evaluating retinal oxygen saturation in NTG, both Michelson & Scibor (2006) and Ito et al. (2008) demonstrated altered retinal oxygen saturation in NTG eyes compared with healthy eyes. Michelson and Scibor specifically found decreased retinal SaO_2 in NTG patients. Ito et al. furthermore demonstrated a decrease in average juxtapapillary retinal SO_2 in NTG eyes. However, they could not replicate Michelson and Scibor's finding of decreased retinal SaO_2 specifically; instead, they found no significant difference in retinal SaO_2 between NTG and healthy patients (Ito et al. 2008). It appears to us that no study to date has replicated Michelson and Scibor's findings of decreased retinal SaO_2 in NTG, suggesting that their aberrant findings may have been an artefact of the early prototype technology used, rather than a reflection of true differences in oxygen saturation. Nor does it appear that any study has replicated the decreased mean retinal saturation observed by Ito et al., possibly for similar reasons: Olafsdottir et al. (2014) suggest that the lack of precise resolution and difficulty distinguishing between capillary and choroid circulations with the early spectral imaging system used by Ito et al. may account for their findings. More recent research using refined technology, including data from the Leuven Eye Study (Abegão Pinto et al. 2016), have consistently shown no significant difference in retinal SaO_2 in NTG eyes compared with healthy eyes (Olafsdottir et al. 2014; Cheng et al. 2016; Yap et al. 2017). It therefore appears that, as with POAG eyes in general, NTG eyes do not exhibit a difference in retinal SaO_2 compared with healthy eyes.

The Leuven Eye Study provides the most robust data regarding retinal SvO_2 and AVO_2 in NTG. An analysis of their data by Abegão Pinto et al. (2016) demonstrated an increase in retinal SvO_2 and a decrease in retinal AVO_2 in NTG eyes. Barbosa-Breda et al. (2019) further note that the AVO_2 in NTG eyes from the Leuven Eye Study is smaller than that of HT-POAG eyes. On the other hand, other studies have found no difference in retinal SvO_2 or AVO_2 between NTG and healthy eyes (Michelson & Scibor 2006; Cheng et al. 2016). There does not appear to be an obvious explanation for the discrepancy between the findings of these studies, though the differences may again be due to variations in RBF and anatomic factors such as retinal pigmentation. Nevertheless, as RBF is frequently decreased in NTG (Fan et al. 2015; Abegão Pinto et al. 2016), findings of either increased or normal SvO2 in NTG are both consistent with abnormally reduced metabolic demand in the retinal tissue (Tables 1 and 2).

Retinal oxygenation in primary angle-closure glaucoma

Two recent studies have evaluated retinal oxygen saturation in primary angle-closure glaucoma (PACG). Cheng et al. (2016) found an increase in SaO_2 in PACG eyes compared with healthy eyes, a finding they also observed in PACG eyes of greater versus lesser disease severity in patients with asymmetric disease. They found no difference between retinal SvO_2 or AVO_2 in PACG eyes compared with normal, POAG and NTG eyes. Finally, they observed decreased arteriolar and venular diameter in PACG eyes. Interestingly, they suggest that the observed increased retinal SaO_2 seems to imply paradoxically increased metabolic demand in PACG, contrary to what is seen in POAG. However, a later study by Yap et al. (2017) did not demonstrate a significant difference in retinal AVO_2 between hemifields of differing disease severity in PACG eyes. More research is required on retinal oxygenation in PACG to further delineate the role of oxygen supply and metabolism, especially compared with POAG (Table 3).

The effects of glaucoma therapy on retinal oxygenation

Therapies proven to slow glaucomatous progression may be expected to have some effect on oxygen delivery to the ONH given the vascular abnormalities observed in POAG. However, there has been limited investigation into the effects of POAG therapy on retinal oxygen saturation in human subjects (Tobe et al. 2013). Carbonic anhydrase inhibitor (CAI) therapy is the only medical treatment that has been specifically examined by multiple studies in this regard. CAIs are thought to increase oxygenation of the optic nerve by CO_2-induced vasodilation of the retinal vasculature (Stefansson et al. 2005) and consequently increased blood flow to the ONH (Rassam et al. 2011). It has been shown that treatment with CAIs results in increased retinal oxygen tension (Stefansson et al. 1999; la Cour et al. 2000; Pedersen et al. 2005) and RBF (Pedersen et al. 2005) in pig eyes, though many of these studies involved the use of large intravenous doses that are not representative of the usual dosing in human patients.

A crossover study in human subjects by Siesky et al. (2008) demonstrated that CAI therapy with topical brinzolamide and dorzolamide eye drops both significantly increased retinal capillary blood flow, consistent with previous findings (Rassam et al. 2011), and increased retinal oxygen saturation. However, neither brinzolamide nor dorzolamide resulted in an increase in retinal SaO_2. Subsequently, Siesky et al. (2010) again demonstrated an increase in RBF with the addition of dorzolamide to timolol monotherapy. The influence of dorzolamide on RBF may help explain the increase in SvO_2 as elevated SvO_2 in POAG eyes has been shown to manifest independently of disease severity (Hammer et al. 2016). Traustason et al. (2009) further observed a decrease in retinal SaO_2 following a switch from initial dual therapy with dorzolamide and timolol to subsequent timolol monotherapy, suggesting a decrease in oxygen supply. Surprisingly, however, they found that the addition of dorzolamide to initial timolol monotherapy in a separate group had no effect on retinal SaO_2, SvO_2 or AVO_2. As oxygen delivery to the retina is approximately equal to the product of AVO_2 and RBF, Traustason et al. suggest that their findings, taken in combination with the those of Siesky et al. (2009), may be interpreted as evidence of increased retinal oxygen supply with CAI treatment, as the combined data show either no change or an increase in AVO_2, respectively, alongside an increase in RBF in treated patients (Traustason et al. 2009).

In addition to the above studies on CAIs, a single study has been

Table 1. Studies of retinal oxygen saturation in primary open-angle glaucoma and healthy eyes

						Oxygen saturation (%), mean ± SD					
Study	Oximeter	Population	Groups		No. Eyes	SaO_2	p	SvO_2	p	AVO_2	p
Michelson & Scibor, (2006)	Prototype dual-wave spectrometer[†]	Patients of the University of Erlangen, Germany	Healthy		58	92.3 ± 3.4	–	55.7 ± 6.8	–	36.6 ± 7.0	–
			NTG		49	**89.7 ± 5.4**	0.006	56.0 ± 8.3	NS	33.7 ± 10.6	NS
			HT-POAG		45	91.4 ± 4.0	NS	58.3 ± 10.5	NS	33.1 ± 11.5	NS
Goharian et al, (2014)	Oxymap	Unspecified	Healthy		22	90.1 ± 4.9	–	45.4 ± 11.0	–	42.1 ± 6.2	–
			POAG		23	92.9 ± 6.7	0.11	48.0 ± 7.7	0.36	**47.6 ± 8.2**	0.015
Mordant et al, (2014)	Novel, validated hyperspectral imaging system	Patients of the Cheltenham and Gloucester General Hospitals, United Kingdom	Healthy		14	104.8 ± 18.7	–	27.9 ± 9.9	–	–	–
			POAG								
			- Better eye		11	98.1 ± 13.7	0.31	**48.2 ± 21.6**	0.03	–	–
			- Worse eye			106.0 ± 22.0	0.89	**42.6 ± 18.8**	0.01	–	–
Olafsdottir et al, (2014)	Oxymap[‡]	Patients of the University Hospitals Leuven, Belgium and the National University Hospital of Iceland, Iceland	Healthy		89	93.3 ± 4.1	–	53.8 ± 6.4	–	39.5 ± 5.7	–
			POAG								
			- All		74	94.1 ± 3.1	0.16	55.5 ± 7.1	0.16	38.5 ± 6.5	0.24
			- MD ≤ 5 dB		33	94.2 ± 3.2	0.26	53.8 ± 7.6	0.87	40.4 ± 7.0	0.75
			- MD ≥ 10 dB		21	94.5 ± 2.4	0.19	**58.2 ± 5.4**	0.0054	**36.4 ± 4.7**	0.021
Ramm et al, (2014)	Vesselmap[§]	Patients of the University of Jena Medical Center, Germany	Healthy		40	97.31 ± 4.84	–	59.78 ± 8.47	–	37.53 ± 6.95	–
			POAG		41	97.43 ± 4.43	0.909	**64.36 ± 7.11**	0.01	**33.07 ± 5.24**	0.002
Sehi et al., (2014a,2014b)	Oxymap	Unspecified	Healthy		22	90.1 ± 4.9	–	48.0 ± 7.7	–	42.1 ± 6.2	–
			POAG		23	92.9 ± 6.7	0.11	45.4 ± 11	0.36	**47.6 ± 8.2**	0.015
Van Keer et al, (2015)	Oxymap	Patients of the University Hospitals Leuven, Belgium	Healthy		54	92.3 ± 3.0	–	55.4 ± 4.6	–	36.8 ± 3.8	–
			POAG		49	**95.1 ± 3.3**	<0.001	**60.8 ± 6.3**	<0.001	**34.4 ± 6.0**	0.014
Abegão Pinto et al, (2016)	Oxymap	Patients of the University Hospitals Leuven, Belgium	Healthy		140	95.5 ± 6.2	–	58.8 ± 7.0	–	36.8 ± 7.1	–
			HT-POAG		214	97.0 ± 16.4	NS	59.2 ± 13.8	NS	37.9 ± 12.7	NS
			NTG		192	96.2 ± 10.1	NS	**62.4 ± 12.5**	0.005	**33.8 ± 12.2**	0.02
Cheng et al, (2016)	Oxymap	Patients of the Singapore National Eye Centre, Singapore	Healthy		38	94.8 ± 7.4	NS	51.9 ± 9.9	NS	42.8 ± 8.8	NS
			HT-POAG		41	102.8 ± 16.0	NS	53.7 ± 13.2	NS	49.1 ± 16.6	NS
			NTG		41	99.4 ± 13.2	NS	55.0 ± 13.1	NS	44.5 ± 13.8	NS
Hammer et al, (2016)	Vesselmap	Unspecified	Inferior Retina	Healthy	50	96.6 ± 5.4	–	58.8 ± 10.6	–	–	–
				POAG	45	97.0 ± 5.4	NS	59.6 ± 9.6	NS	–	–
			Nasal Retina	Healthy	50	99.9 ± 4.3	–	63.1 ± 7.8	–	–	–
				POAG	45	99.4 ± 3.9	NS	64.2 ± 6.5	NS	–	–
			Superior Retina	Healthy	50	96.4 ± 5.1	–	57.2 ± 8.5	–	–	–
				POAG	45	97.1 ± 5.6	NS	**61.2 ± 7.8**	≤0.05	–	–
Shahidi et al, (2017)	Prototype hyperspectral laser imaging system[¶]	Patients of the Toronto Western Hospital, Canada	Healthy		17	92.97 ± 1.56	–	55.90 ± 4.78	–	37.7 ± 5.15	–
			POAG								
			- All		22	95.11 ± 4.36	0.062	56.93 ± 8.30	0.727	39.03 ± 8.40	0.376
			- MD <−6 dB		13	94.62 ± 5.81	NS	62.40 ± 7.39	NS	33.60 ± 7.21	NS
			- MD ≥−6 dB		9	95.45 ± 3.23	NS	**33.60 ± 7.21**	≤0.05	42.78 ± 7.18	NS

Table 1. (Continued)

Study	Oximeter	Population	Groups	No. Eyes	Peripapillary oxygen saturation (%), mean ± SD							
					Superior	p	Nasal	p	Infero-temporal	p	Average	p
Ito et al, (2008)	Fourier transform-based spectral retinal imaging system[††]	Japanese patients	Healthy	20	89 ± 11	–	92 ± 9	–	86 ± 10	–	88 ± 8	–
			HT-POAG	41	**84 ± 11**	0.0029	**85 ± 14**	0.048	**80 ± 12**	0.039	**82 ± 10**	0.039
			NTG	15	**77 ± 10**	0.009	**77 ± 11**	0.019	**73 ± 11**	0.001	**78 ± 8**	0.002

P = significance of difference between patients and controls. Statistically significant differences ($p \leq 0.05$) are shown in bold.
AVO_2 = arterio-venous oxygen saturation gradient, HT-POAG = high-tension primary open-angle glaucoma, MD = visual field mean defect, NS = not significant, NTG = normal tension glaucoma, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, SaO_2 = retinal arteriolar oxygen saturation, SD = standard deviation, SvO_2 = retinal venular oxygen saturation.
† University of Jena, Germany.
‡ Oxymap Retinal Oximeter; Oxymap ehf, Reykjavik, Iceland.
§ Vesselmap Retinal Oximeter; Imedos Systems GmbH, Jena, Germany.
¶ University Health Network, Toronto Western Hospital, Toronto, Canada.
†† Retinal Cube; ASI Co., Migdal HaEmek, Israel.

conducted to assess the effect of surgical POAG treatment retinal oxygen saturation. Hardarson et al. 2009 evaluated the effects of trabeculectomy and Ahmed tube shunt surgery on patients with glaucoma (POAG and exfoliative). In contrast to the reported effects of carbonic anhydrase therapy, they found a slight postsurgical increase in SaO_2 but no significant postsurgical changes in retinal AVO_2 or SvO_2 in treated eyes; however, they did not measure RBF.

Together, the literature on medical and surgical POAG therapy paints a mixed picture of the effects of POAG treatment on retinal oxygenation. Evidence that medical therapy with CAIs works to increase oxygen delivery to the ONH may be consistent with the vascular ischaemic hypothesis of POAG pathogenesis. On the other hand, it appears that surgical filtration therapy, which results in the most dramatic IOP reduction, has no significant effect on AVO_2 or SvO_2 despite having a well-substantiated impact on disease progression. It is important to note that all of these studies to date have been small and the conclusions drawn are tentative. Moreover, it is difficult to assign significance to small changes in retinal oxygenation with treatment, and it is unclear to what degree the findings can be interpreted in relation to the vascular hypothesis of glaucoma pathogenesis. Further research is necessary to more clearly elucidate the effects of POAG treatment on oxygen delivery to the ONH and the implications for glaucoma pathogenesis.

Mathematical models of retinal oxygenation in glaucoma

Practical difficulties such as the inaccessibility of ocular tissues hinder detailed experimental investigations into the causal factors influencing oxygen delivery in POAG. Animal models allow certain obstacles to be circumvented by enabling the manipulation of variables such as RBF or IOP in an attempt to induce glaucomatous changes. Yet, questions remain regarding the appropriate translation of findings in animal models to our understanding of human disease. Mathematical models developed from

Table 2. Studies of retinal oxygen saturation in primary open-angle glaucoma eyes of varying disease severity

Study	Oximeter	Population		Groups		No. eyes	Oxygen saturation (%), mean ± SD					
							SaO_2	p	SvO_2	p	AVO_2	p
Olafsdottir et al, 2011	Oxymap[†]	POAG patients of the Augnlæknar Reykjavíkur Clinic, Iceland		Good VF (−2 < MD < 2 dB)		12	99 ± 4	0.38	**62 ± 3**	0.0018	**37 ± 4**	0.003
				Poor VF (MD > 10 dB)		9	98 ± 3	0.38	**68 ± 4**	0.0018	**30 ± 4**	0.003
Mordant et al, 2014	Novel, validated hyperspectral imaging system	POAG patients of the Cheltenham and Gloucester General Hospitals, United Kingdom		Better eye		11	98.1 ± 13.7	0.33	48.2 ± 21.6	0.53	–	–
				Worse eye			106.0 ± 22.0	0.33	42.6 ± 18.8	0.53	–	–
Olafsdottir et al, 2014	Oxymap	POAG patients of the University Hospitals Leuven, Belgium and the National University Hospital of Iceland, Iceland		Good VF (MD ≤ 5 dB)		33	94.2 ± 3.2	0.68	**53.8 ± 7.6**	0.026	**40.4 ± 7.0**	0.035
				Poor VF (MD ≥ 10 dB)		21	94.5 ± 2.4	0.68	**58.2 ± 5.4**	0.026	**36.4 ± 4.7**	0.035
Vandewalle et al, 2014	Oxymap	POAG patients of the University Hospitals Leuven, Belgium		Good VF (MD> −6 dB)		29	97 ± 2	0.3	**65 ± 6**	0.003	**33 ± 6**	0.002
				Poor VF (MD < −12 dB)		14	98 ± 2	0.3	**69 ± 3**	0.003	**29 ± 3**	0.002
Cheng et al, 2016	Oxymap	Patients of the Singapore National Eye Centre, Singapore		HT-POAG	Better eye	68	99.7 ± 13.9	0.14	53.0 ± 12.4	0.12	46.7 ± 13.9	0.5
					Worse eye		104.9 ± 16.6	0.14	55.1 ± 13.2	0.12	49.8 ± 16.9	0.5
				NTG	Better eye	70	98.7 ± 12.0	0.96	54.7 ± 10.5	0.52	43.9 ± 12.3	0.82
					Worse eye		99.3 ± 15.7	0.96	55.5 ± 13.9	0.52	44.3 ± 16.3	0.82
Shimazaki et al, 2016	Oxymap	POAG patients of the Kagawa University Hospital, Japan		Difference between hemifield MDs > 10 dB	Better hemifield	44	104 ± 11.8	0.75	**55.4 ± 7.2**	< 0.01	**48.6 ± 11.4**	0.02
					Worse hemifield		103 ± 23.3	0.75	**59.0 ± 8.0**	< 0.01	**44.4 ± 9.0**	0.02
				Difference between hemifield MDs < 5 dB	Better hemifield	40	99.3 ± 9.3	0.25	58.2 ± 6.9	0.74	41.0 ± 9.3	0.21
					Worse hemifield		100.5 ± 9.5	0.25	58.0 ± 7.4	0.74	42.6 ± 7.6	0.21
Shahidi et al, 2017	Prototype hyperspectral laser imaging system[‡]	Patients of the Toronto Western Hospital, Canada		Mild POAG (MD ≥ −6)		22	94.62 ± 5.81	NS	**62.40 ± 7.39**	≤ 0.05	**33.60 ± 7.21**	≤ 0.05
				Severe POAG (MD < −6)			95.45 ± 3.23	NS	**33.60 ± 7.21**	≤ 0.05	**42.78 ± 7.18**	≤ 0.05
Yap et al, 2017	Oxymap	Patients of the Singapore National Eye Centre, Singapore		All POAG	Better hemifield	99	103.3 ± 15.7	0.38	54.3 ± 14.8	0.69	49.0 ± 17.6	0.29
					Worse hemifield		99.7 ± 37.8	0.38	55.2 ± 16.5	0.69	44.4 ± 39.0	0.29
				HT-POAG	Better hemifield	37	–	–	–	–	51.5 ± 18.0	0.85
					Worse hemifield		–	–	–	–	51.2 ± 22.2	0.85
				NTG	Better hemifield	34	–	–	–	–	47.3 ± 15.3	0.42
					Worse hemifield		–	–	–	–	44.0 ± 18.0	0.42
Shimazaki et al, 2018	Oxymap	Patients of the Kagawa University Hospital, Japan	HT-POAG	Difference between hemifield MDs ≤ 5 dB	Better hemifield	25	100.2[§]	0.90	55.1[§]	0.38	–	–
					Worse hemifield		99.8[§]	0.90	54.7[§]	0.38	–	–
				Difference between hemifield MDs ≥ 10 dB	Better hemifield	19	105.8[§]	0.78	**52.6**[§]	0.001	–	–
					Worse hemifield		105.0[§]	0.78	**56.7**[§]	0.001	–	–
			NTG	Difference between hemifield MDs ≤ 5 dB	Better hemifield	22	100.7[§]	0.53	**54.7**[§]	0.004	–	–
					Worse hemifield		101.9[§]	0.53	**57.9**[§]	0.004	–	–
				Difference between hemifield MDs ≥ 10 dB	Better hemifield	26	101.0[§]	0.68	**53.2**[§]	0.04	–	–
					Worse hemifield		103.7[§]	0.68	**56.7**[§]	0.04	–	–

P = significance of difference between groups of different severity. Statistically significant differences ($p \leq 0.05$) are shown in bold. Statistically significant differences ($p \leq 0.05$) are shown in bold.
AVO_2 = arterio-venous oxygen saturation gradient, HT-POAG = high-tension primary open-angle glaucoma, MD = visual field mean defect, NS = not significant, NTG = normal tension glaucoma, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, SaO_2 = retinal arteriolar oxygen saturation, SD = standard deviation, SvO_2 = retinal venular oxygen saturation.
[†] Oxymap Retinal Oximeter; Oxymap ehf, Reykjavik, Iceland.
[‡] University Health Network, Toronto Western Hospital, Toronto, Canada.
[§] Median value.

Table 3. Studies of retinal oxygen saturation in primary angle-closure glaucoma

Study	Oximeter	Population	Groups	No. eyes	Oxygen saturation (%), mean ± SD					
					SaO_2	p	SvO_2	p	AVO_2	p
Cheng et al, (2016)	Oxymap[†]	Patients of the Singapore National Eye Centre, Singapore	Healthy	38	94.8 ± 7.4	–	51.9 ± 9.9	–	42.8 ± 8.8	–
			PACG	39	**104.7 ± 16.4**	0.048	54.3 ± 13.7	NS	50.4 ± 17.9	NS
			Asymmetric PACG -Better eye	64	**97.4 ± 9.2**	0.03	53.6 ± 13.6	0.75	**50.9 ± 17.9**	0.04
			-Worse eye		**103.5 ± 17.3**	0.03	53.7 ± 14.2	0.75	**42.4 ± 12.4**	0.04
Yap et al, (2017)	Oxymap	PACG patients of the Singapore National Eye Centre, Singapore	Better hemifield	28	–	–	–	–	46.8 ± 19.9	0.41
			Worse hemifield		–	–	–	–	36.2 ± 65.4	0.41

Statistically significant differences ($p \leq 0.05$) are shown in bold.
AVO_2 = arterio-venous oxygen saturation gradient, HT-POAG = high-tension primary open-angle glaucoma, NS = not significant, NTG = normal tension glaucoma, PACG = primary angle-closure glaucoma, POAG = primary open-angle glaucoma, SaO_2 = retinal arteriolar oxygen saturation, SD = standard deviation, SvO_2 = retinal venular oxygen saturation.
[†] Oxymap Retinal Oximeter; Oxymap ehf, Reykjavik, Iceland.

human patient data provide a unique and valuable experimental tool for investigating the variables that influence human physiology and lead to pathological disturbances in vivo. By manipulating specific variables and comparing the resulting data produced to the data obtained from human patients, researchers can use these empirically informed models to test pathophysiologic hypotheses and identify causal factors that may underlie observed pathology (Woodward 1997).

Recently, mathematical models of ocular haemodynamics have been used to investigate the role of RBF regulation and oxygenation in POAG. Arciero et al. (2013) developed a model based on vascular wall mechanics and haemodynamic relationships, similar to previous models (Carlson et al. 2008), to predict the role of myogenic, shear stress, conducted metabolic and carbon dioxide vascular responses in regulating RBF in both healthy and POAG cases. This was the first model of RBF to account for both IOP and autoregulatory mechanisms (Arciero et al. 2013). The model was validated by demonstrating that its predictions of blood velocity and flow values for different sized vessels as well as autoregulation (flow versus pressure) were consistent with published clinical data. As expected, the model predicted a decline in SvO_2 as arterial blood pressure was decreased and metabolic oxygen demand was held constant (Arciero et al. 2013). The model provides a very useful framework for studying the relationship between blood flow and oxygenation in the retina, but it does not investigate the relationship between SvO_2 and disease severity.

Carichino et al. (2016) used this 2013 model to predict possible mechanisms that can result in SvO_2 variations in POAG eyes. Their model simulated the effect of varying numerous vascular and metabolic factors on retinal venous oxygen saturation, and three possible mechanisms that could lead to increased SvO_2 were identified. First, decreased tissue metabolic oxygen demand led to an increase in SvO_2. Second, an increase in SvO_2 was predicted for some values of OPP if the conducted metabolic and carbon dioxide autoregulatory mechanisms were impaired. Last, a decrease in the volume of tissue assumed to be supplied by each capillary or arteriole (such as would occur with increased capillary density) also led to an increase in SvO_2 (Carichino et al. 2016). Importantly, however, they noted that the last finding is not consistent with clinical observations of POAG retinas, which instead demonstrate decreased retinal vascular density (Yarmohammadi et al. 2016). Thus, the model predictions suggest that either decreased metabolic oxygen demand or impaired vascular autoregulatory mechanisms, or some combination of the two, may contribute to the increase in SvO_2 that has been observed in POAG.

Carchino et al. compared their theoretical predictions with clinical data from Olafsdottir et al. (2014). Patient-specific parameters (e.g. SaO_2, IOP and MAP) were used in individual model simulations, and the model-predicted level of SvO_2 was compared with the actual measured SvO_2 from the same patient. Multiple simulations were run to determine the values of oxygen demand, degree of impaired autoregulation or tissue volume that would lead to the clinically observed SvO_2 values. This analysis was performed on healthy, advanced HT-POAG and advanced NTG eyes at OPP values specific to each patient. Interestingly, they found that decreased oxygen metabolism could account for the increase in SvO_2 in HT-POAG patients only; no significant change in SvO_2 was predicted when oxygen metabolism was artificially decreased in simulations on data from NTG patients. On the other hand, an increase in SvO_2 in NTG simulations was only obtained by impairing vascular autoregulation.

Most recently, Fry et al. (2018) developed a retinal model, based on confocal microscopy images of the mouse retina, that accounts for the heterogeneous network structure of the retinal vasculature. The model is used to predict oxygen tension (PO_2) in the arteriolar vessels and surrounding tissue at varying levels of metabolic oxygen demand. The average vessel PO_2 was shown to decrease as metabolic oxygen demand was increased. However, the standard deviation of PO_2 in the vessels was predicted to nearly double as oxygen demand was increased from 1 to 8 cm^3 $O_2/100$ cm^3/min, indicating the presence of a wide spread of local PO_2 values that cannot be identified when using

average PO_2 as an indicator of retinal oxygenation. In cases of high oxygen demand, some terminal arterioles may have abnormally low PO_2 levels that can create areas of poor oxygenation in the downstream capillary bed. However, this effect of elevated oxygen demand would remain undetected if average PO_2 were used as the sole indicator of oxygenation. Thus, the model highlights the importance of precise arteriolar oxygen measurements in retinal oximetry in order to detect areas of local hypoxemia that might otherwise go undetected using current spectroscopic retinal oximetry technology to measure average regional oxygenation. It also highlights an important limitation of simplified, nonheterogeneous models of retinal vasculature, which may not be sensitive to highly localized areas of hypoxia.

These mathematical models provide important insight into the altered retinal oxygenation and vascular changes in POAG. The findings of Carchino et al. (2016) suggest that two different mechanisms may be at play, giving rise to two different types of POAG: HT-POAG and NTG. The models suggest that decreased oxygen metabolism due to retinal tissue atrophy gives rise to elevated SvO_2 in HT-POAG. Conversely, the models suggest that in NTG (i.e. in the absence of elevated IOP and mechanical stress), vascular dysregulation may be the primary factor leading to unstable oxygen delivery and either ischaemic or oxidative perfusion-reperfusion injury, with resultant tissue atrophy.

Summary

The pathophysiology of POAG remains a topic of considerable discussion. Evaluation of retinal oxygen saturation can play an important role in untangling the various proposed pathogenic mechanisms underlying the disease process. Two broad, nonmutually exclusive hypotheses have been described to explain the development of POAG: a mechanical and a vascular hypothesis. The mechanical hypothesis holds that chronically elevated IOP induces POAG by mechanical stress upon the lamina cribrosa and ONH, while the vascular hypothesis suggests that abnormal blood flow to the ONH and retina primarily drive the development of POAG.

The presence of vascular irregularities and decreased RBF in POAG has been widely established in the literature. Both the vascular and mechanical hypotheses are consistent with this finding: vascular irregularities may result in either chronic or intermittent ischaemia as a driver of disease progression, while elevated IOP may cause tissue atrophy and consequent vascular abnormalities. Clarifying whether these vascular changes constitute the primary causal aetiology of POAG, or are secondary effects of decreased metabolic oxygen demand in primarily atrophic retinal tissue is therefore a key question in delineating the pathogenic role of these two mechanisms.

As AVO_2 is proportional to the ratio of metabolic oxygen demand to blood flow ($AVO_2 \propto \frac{\text{oxygen metabolism}}{\text{RBF}}$), an assessment of retinal SaO_2 and SvO_2 in POAG, combined with an understanding of RBF in POAG, can provide important information regarding oxygen supply and metabolism in POAG. Two-wave spectroscopic retinal oximetry is a tool that has been developed for the detailed and noninvasive study of retinal oxygen saturation. This technology has yielded promising data, and certain trends have been established across the literature.

Data on retinal SaO_2 in POAG patients largely indicate that retinal SaO_2 is unchanged in cases of POAG and is not associated with disease severity. While this finding suggests that the oxygen content of the blood supply to the retina is not affected in glaucoma, it does not rule out chronic ischaemia due to decreased RBF. Moreover, underlying intermittent ischaemia has been identified as a potential driver for the disease process by reperfusion injury. As it is not currently possible to continuously monitor retinal oxygen saturation with spectroscopic retinal oximetry, irregular variations in RBF and inconsistent oxygen supply to the retina and ONH may remain undetected by current technology.

The data regarding retinal AVO_2 is conflicting: certain studies have found no change in AVO_2, while others have observed a decrease in AVO_2 in POAG eyes. A decrease in AVO_2 may reflect a decrease in metabolic oxygen demand in the context of normal or only slightly decreased blood flow. On the other hand, normal AVO_2 may also be consistent with a decrease in oxygen metabolism if the decrease is balanced by a proportional decrease in RBF, which is not unlikely given that significantly decreased RBF has been well-documented in glaucoma. Thus, taken together, the data on AVO_2 may suggest that there is an overall decrease in oxygen metabolism in glaucoma, reflecting tissue atrophy. However, further research with concurrent measurements of RBF and retinal oxygenation is required to more accurately assess retinal oxygen metabolism (Werkmeister et al. 2015). This approach has previously been employed in the study of retinal oxygen metabolism in diabetes (Fondi et al. 2017) and in response to visual stimulation (Palkovits et al. 2015).

The effects of POAG therapy on oxygen metabolism are currently insufficiently investigated. Limited pilot investigations suggest CAIs may increase oxygen metabolism, possibly through modulating an increase in RBF. Significant research is currently required to understand how various pharmaceutical and surgical interventions may influence tissue metabolism and retinal oxygen consumption, and how these physiologic changes may alter the course of glaucoma.

Mathematical models may help to make sense of the retinal oximetry data reported in the literature by suggesting two different pathophysiologic mechanisms for POAG, paralleling the two types of POAG (HT-POAG and NTG) and leading to the same end result of normal or decreased AVO_2 with preserved SaO_2. These models suggest that decreased oxygen metabolism may arise secondary to primarily atrophic tissue in HT-POAG, consistent with the hypothesis that mechanical stressors are the primary pathogenic force driving glaucomatous progression in this type of glaucoma. Conversely, the models suggest that impaired vascular autoregulation may be the primary pathogenic factor underlying the development of NTG. As intact autoregulation is crucial for constant and stable RBF, impaired autoregulatory mechanisms would be expected to result in intermittent ischaemia and consequent reperfusion injury due to oxidative stress. In this case, oxygen demand decreases in proportion to tissue atrophy as the disease progresses, consistent with the oximetry findings in NTG eyes.

Additional research is necessary to corroborate these findings and further delineate the role of vascular and mechanical factors in the pathogenesis of glaucoma. In particular, future studies concurrently measuring RBF and retinal oxygenation will be of great value in the accurate estimation of retinal oxygen metabolism in POAG. Longitudinal studies are also required to establish causal relationships between metabolic oxygen demand, RBF and glaucomatous tissue atrophy. Finally, technological advances in oximetric imaging modalities will ideally allow for more specificity of observed outcomes in future studies. The continued study of retinal oxygen saturation in POAG holds the potential to help identify new therapeutic targets, develop improved treatments and meaningfully enhance our understanding of this decidedly complex disease.

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