



## REVIEW

# Reactive oxygen species, oxidative stress, glaucoma and hyperbaric oxygen therapy



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**Abstract** This review examines the role of oxidative stress in damage to cells of the trabecular meshwork and associated impaired aqueous drainage as well as damage to retinal ganglion cells and associated visual field losses. Consideration is given to the interaction between vascular and mechanical explanations for pathological changes in glaucoma. For example, elevated intraocular pressure (IOP) forces may contribute to ischaemia but there is increasing evidence that altered blood flow in a wider sense is also involved. Both vascular and mechanical theories are involved through fluctuations in intraocular pressure and dysregulation of blood flow. Retinal function is very sensitive to changes in haemoglobin oxygen concentration and the associated variations in the production of reactive oxygen species. Reperfusion injury and production of reactive oxygen species occurs when IOP is elevated or blood pressure is low and beyond the capacity for blood flow autoregulation to maintain appropriate oxygen concentration. Activities such as those associated with postural changes, muscular effort, eye wiping and rubbing which cause IOP fluctuation, may have significant vascular, mechanical, reperfusion and oxidative stress consequences. Hyperbaric oxygen therapy exposes the eye to increased oxygen concentration and the risk of oxidative damage in susceptible individuals. However, oxygen concentration in aqueous humour, and the risk of damage to trabecular meshwork cells may be greater if hyperbaric oxygen is delivered by a hood which exposes the anterior ocular surface to higher than normal oxygen levels. Oronasal mask delivery of hyperbaric oxygen therapy appears to be indicated in these cases.

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**PALABRAS CLAVE**

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**Especies reactivas de oxígeno, estrés oxidativo, glaucoma y terapia de oxígeno hiperbárico**

**Resumen** Esta revisión examina el papel del estrés oxidativo en el daño celular de la red trabecular, la disfunción del drenaje acuoso, así como las lesiones de las células ganglionares de la retina y las pérdidas de campo visual asociadas. Se tiene en cuenta la interacción entre las explicaciones a los cambios patológicos en el glaucoma, desde el punto de vista vascular y mecánico. Por ejemplo, la elevación de las fuerzas de la presión intraocular (PIO) puede contribuir a la isquemia, aunque existe evidencia creciente de que también está implicada la alteración del flujo sanguíneo, en un sentido más amplio. También están implicadas las teorías vasculares y mecánicas a través de las fluctuaciones de la PIO y la desregulación del flujo sanguíneo. La función de la retina es muy sensible a los cambios de la concentración de oxígeno en la hemoglobina y a las variaciones asociadas a la producción de especies reactivas de oxígeno. Las lesiones por reperusión y la producción de especies reactivas de oxígeno se producen cuando la PIO es elevada o cuando la presión sanguínea es baja, y sobrepasa la capacidad de autoregulación del flujo sanguíneo para mantener la concentración de oxígeno adecuada. Las actividades tales como las asociadas a cambios posturales, esfuerzo muscular, lavado y frotamiento de ojos, que causan fluctuación de la PIO, pueden tener repercusiones considerables de tipo vascular y mecánico, y de reperusión y estrés oxidativo. La terapia de oxígeno hiperbárico expone al ojo a un incremento de la concentración de oxígeno y al riesgo de daño oxidativo en individuos susceptibles. Sin embargo, la concentración de oxígeno en el humor acuoso y el riesgo de lesiones de las células de la red trabecular pueden ser superiores cuando el oxígeno hiperbárico es liberado por una campana que expone la superficie ocular anterior a unos niveles de oxígeno más elevados de lo normal. La liberación de oxígeno hiperbárico mediante mascarilla oronasal parece más indicada en estos casos.

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The glaucomas are a worldwide leading cause of irreversible vision loss.<sup>1</sup> They can be viewed as neurodegenerative diseases which, like other conditions such as Alzheimer's or Parkinson's disease, are ultimately caused by deficits in neuronal function.<sup>2</sup> For example, the glaucomas are characterised by progressive degeneration of retinal ganglion cells (RGC)<sup>1</sup> and their axons.<sup>3</sup> As RGCs cannot divide or regenerate, optic nerve damage appears to be irreversible.<sup>3</sup> The molecular basis for RGC death is complex and includes axonal transport failure, neurotrophic factor deprivation and oxidative stress, for example.<sup>2</sup> It is likely that several molecular pathways converge to induce RGC loss.<sup>2</sup>

**Mechanical and vascular explanations for glaucomatous pathology**

According to the mechanical theory of glaucoma, increased intraocular pressure (IOP) can be a consequence of abnormal resistance to aqueous humour drainage via the trabecular meshwork.<sup>4</sup> The mechanical theory stresses the importance of direct IOP-related increased compression of the axonal fibres and support structures of the anterior optic nerve, with distortion of the lamina cribrosa plates and interruption of axoplasmic flow, resulting in death of the RGCs.<sup>5</sup> Compression of the anterior optic nerve is also a function of intracranial pressure which may vary in

concert with, or independently of IOP fluctuations.<sup>6</sup> However, apart from mechanical stress elevated IOP-related factors also trigger initial neuronal damage in glaucoma through ischaemic injury processes.<sup>6,7</sup> The vascular theory focuses on the development of intraneural ischaemia resulting from decreased optic nerve perfusion.<sup>5</sup> Causes of decreased blood flow include mechanical compression of vessel walls,<sup>8</sup> for example. Mechanical stress could detrimentally affect blood supply to the laminar segments of the axons through deformation of the capillary-containing laminar beams.<sup>9</sup> This model is consistent with the results of Gottanka and coauthors who found a loss of capillaries supplying the optic nerve (ON) in primary open angle glaucoma (POAG).<sup>10</sup>

However, there is increasing evidence that altered blood flow in a wider sense may play a major role in the pathogenesis of OAG.<sup>11</sup> Autoregulation is a manifestation of local blood flow regulation being the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure.<sup>12</sup> Vascular dysregulation interferes with autoregulation of ocular perfusion and renders the eye to be more sensitive to IOP elevation or blood pressure (BP) reduction.<sup>13</sup> Reduced blood circulation due to vascular dysregulation resulting from IOP fluctuation is more damaging than reduced circulation due to a stable elevated IOP or arteriosclerosis<sup>13</sup> because instability of ocular blood flow leads to reperfusion injury which is mild but

occurs repeatedly.<sup>14</sup> This explanation is supported by the observation of an association between disturbed autoregulation and glaucomatous progression despite IOP being normal<sup>14</sup> when measured clinically.<sup>15</sup> The main cause for insufficient autoregulation is a primary vascular dysregulation syndrome.<sup>14</sup> Primary vascular dysregulation tends to be associated with cold hands, low BP, signs of oxidative stress as well as with diffuse and fluctuating field defects.<sup>16</sup> There is a high prevalence of primary vascular dysregulation in the general population and virtually all organs may be affected with eyes at greater risk for normal tension glaucoma (NTG) and optic disc haemorrhages.<sup>16</sup> An insufficient autoregulation and unstable ocular perfusion with an associated unstable oxygen supply leads to oxidative stress within the axons of the ON due to an increase in reactive oxygen species.<sup>14</sup> The terms oxygen free radicals, oxidative free radicals and reactive oxygen species (ROS) are used interchangeably.<sup>17</sup> Vascular dysregulation can involve inadequate constriction or insufficient dilatation as well as excessive dilatation of arteries, capillaries or veins.<sup>16</sup> Glaucoma patients show signs of reduced ocular blood flow as well as ischaemia which are consistent with vascular dysregulation.<sup>14</sup> In addition to an increased IOP, a thin central cornea and both ethnicity and genetic factors, the main risk factors for glaucomatous damage are IOP fluctuations, low BP, reduced perfusion pressure and fluctuation of perfusion pressure.<sup>16</sup> Ocular blood flow is unstable if either IOP fluctuates above or BP fluctuates below the capacity of autoregulation to maintain flow within normal range.<sup>16</sup> Pressure chamber studies which show that light sensitivity is directly reduced by a reduction in oxygen supply demonstrate retinal dependence on continuity of normal range blood supply with retinal function being rapidly influenced by reduction in oxygen saturation.<sup>18</sup>

### The significance of fluctuations in intraocular pressure

Circadian patterns have been detected for systemic BP, ocular perfusion pressure, and ocular blood flow.<sup>11</sup> NTG patients have significantly greater variability of night time systolic, diastolic and mean arterial pressure compared to control patients.<sup>11</sup> Patients with POAG show a larger diurnal fluctuation of ocular blood flow.<sup>11</sup> These findings suggest that unstable ocular perfusion pressure, rather than a steady reduction in ocular blood flow, can contribute to glaucomatous optic neuropathy.<sup>11</sup> IOP is determined by the balance between secretion of aqueous humour by the ciliary body and its drainage through the trabecular meshwork and the uveoscleral outflow pathway.<sup>19</sup> Elevated IOP is the most important risk factor for POAG development.<sup>1,14,19,20</sup> IOP varies throughout a 24 h period with at least 33% of patients with OAG never have documented elevations of IOP.<sup>11</sup> However, lack of documentation of elevation episodes appears to be due to an over-reliance on consulting room measurements. Sleep laboratory measurements will capture a wider range of fluctuations, for example.<sup>21,22</sup> However, apart from sleep, there are numerous other routine events and habits involving different body orientations, such as different physical activities involving variable degrees of muscular effort

and breathing effort, wearing swimming goggles, playing high wind resistance musical instruments as well as eye rubbing, wiping or touching which indents the ocular surface, all of which are known to elevate IOP.<sup>15</sup> For example, light eye touching approximately doubles IOP and eye rubbing forces can elevate IOP by 100's of mmHg,<sup>15</sup> One of the main risks for glaucomatous damage is IOP fluctuation<sup>16</sup> and episodes of fluctuation which are associated with numerous day to day activities, and which are usually undetected, may increase risk depending on their frequency as well as their duration and the level of elevation involved.<sup>15</sup> The detection and monitoring of these IOP fluctuations which are associated with such activities require a method of 24 h monitoring which does not restrict participation in those activities.<sup>23</sup>

### Oxidative stress

Retinal function is very sensitive to fluctuations in haemoglobin oxygen concentration.<sup>18</sup> Metabolism of oxygen produces reactive oxygen species<sup>14</sup> which form under normal physiological conditions and can be beneficial.<sup>4</sup> Low levels of ROS production, produced mainly by mitochondria, are required to maintain physiological functions including proliferation, host defence, signal transduction and gene expression.<sup>4</sup> However, ROS can also be dangerous.<sup>14</sup> For example, oxidative stress due to excess quantities of reactive oxygen species can cause RGC death.<sup>24</sup> Several concomitant factors such as increased ROS production and imbalance between pro-oxidative and antioxidant capacity have been postulated as the crucial factors in early retinal injury, together with the reduced ocular perfusion pressure in the blood vessels (the vascular theory of glaucoma).<sup>4</sup> Both vascular and mechanical theories help to explain the formation of ROS in glaucoma.<sup>24</sup> The vascular theory is based on ischaemia-induced production of ROS due to compromised blood flow in retinal vessels.<sup>24</sup> The mechanical pressure theory for the formation of ROS involves elevated IOP inhibiting retrograde neurotrophin support for RGC axons.<sup>24</sup> For both mechanisms RGC death is due to oxidative stress.<sup>24</sup> Oxidative stress in glaucoma occurs mainly in the mitochondria of the RGCs and their axons.<sup>16</sup> Production of ROS may be triggered by primary vascular dysregulation as a consequence of unstable blood flow and an associated unstable oxygen supply.<sup>16</sup>

For example, one highly ROS, the hydroxyl radical, is generated during the early phase of reperfusion after ischaemia and is a major cause of retinal injury.<sup>25</sup> Also, malondialdehyde is used as a biomarker for ROS activity being one of the best known secondary products of lipid peroxidation.<sup>26</sup> Blood and aqueous humour malondialdehyde levels in glaucoma patients were found to be significantly higher than in controls.<sup>27</sup> Antioxidants delay or prevent oxidation of a substrate and reduce ROS levels.<sup>14</sup> Analysis of blood plasma samples found that total antioxidant status was decreased in patients with glaucoma, especially in POAG and pseudoexfoliation glaucoma but less so in primary angle-closure glaucoma.<sup>20,27</sup> These findings support the hypothesis that decreased antioxidant defence and/or increased oxidative stress can have a critical role in the pathogenesis of glaucoma.<sup>20</sup>

## Trabecular meshwork

Increased IOP in POAG can be due to an increased resistance of aqueous outflow through the trabecular meshwork.<sup>14</sup> That ROS can play a role in the pathogenesis of glaucoma by stimulating apoptosis and inflammatory pathways on the level of the trabecular meshwork<sup>4</sup> is suggested by the finding that the TM is exposed to ROS in aqueous humour.<sup>14</sup> For example, glaucoma patients display a significant depletion of total antioxidant potential in their aqueous humour.<sup>14,28</sup> Trabecular meshwork cells can be damaged by elevated concentration of oxygen radicals<sup>29</sup> with associated alterations in aqueous drainage.<sup>14</sup>

## Reperfusion injury

Reperfusion injury occurs when blood supply returns to a tissue after a period of ischaemia (anoxia or hypoxia) and ensuing inflammation and oxidative damage cause tissue injury to occur through the production of ROS.<sup>14</sup> Reperfusion injury occurs in patients with a high IOP or a very low BP which exceeds the compensatory capacity of blood flow autoregulation.<sup>14</sup> Consequently, reperfusion injury can also occur in patients with a normal or mildly increased IOP or normal or mildly decreased BP if those subjects suffer from blood flow dysregulation.<sup>14</sup> Retinal ischaemia-reperfusion injury by transient elevation of intraocular pressure in animal models is known to induce necrosis and apoptosis of cells.<sup>25</sup> For example, studies in rats found that retinal ischaemia-reperfusion after transient IOP elevation induced apoptosis of cells in the RGC and inner nuclear layer.<sup>30</sup> Recurrent mild reperfusion leads to a chronic oxidative stress, especially in mitochondria.<sup>14</sup> The loss of neurons due to ischaemia/reperfusion injury can be influenced by many of the conditions that are considered as risk factors in human neurodegenerative diseases such as Alzheimer's or Parkinson's disease.<sup>31</sup> Bagnis and coauthors found that glutamine synthase, nitric oxide synthase, superoxide dismutase and glutathione transferase as measured by antibody microassay, may be useful oxidative markers in the aqueous humour of POAG patients.<sup>19</sup> In addition, increased levels of glutathione peroxidase, and malondialdehyde in human aqueous can be associated with POAG.<sup>32</sup>

## Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) has been successfully used for the treatment of a variety of conditions related to hypoxia, including decompression sickness, acute carbon monoxide intoxication, air embolism, soft tissue infections, radiation necrosis, and impaired wound healing.<sup>33,34</sup> For example, diabetic patients can be compromised as far as wound healing is concerned and adjunctive HBOT can be valuable for treating selected cases of infected and/or hypoxic diabetic foot ulcers.<sup>35,36</sup> Wound healing models have demonstrated that HBOT is beneficial by upregulating vascular endothelial growth factor and associated angiogenesis.<sup>37</sup> A review of the literature found that in addition to cataract, age-related macular degeneration and keratoconus, there may be other ocular diseases for which the pathology involves reactive oxygen species and so for which

exposure to HBOT-related oxidative stress could be significantly adverse.<sup>38</sup>

For example, a patient with a ruptured retinal arterial macroaneurysm experienced acute development of severe macular oedema two days after the seventh HBOT treatment.<sup>37</sup> Yonekawa and coauthors recommended that HBOT could be contraindicated for retinovascular diseases.<sup>37</sup> The involvement of oxidative stress in glaucomatous pathology<sup>1,7,28,29,39</sup> suggests that patients with glaucoma could be contraindicated for HBOT. Alternatively, depending on the strength of an indication for HBOT, this form of treatment for a patient with glaucoma may proceed cautiously with progressive monitoring for any adverse effects. Studies in rats found that ageing is the most significant risk factor for the loss of RGCs.<sup>31</sup> As the animal ages, there is an inherent loss of RGCs and when the older eye is exposed to retinal ischaemia/reperfusion stress, a greater percentage of the remaining cells degenerate.<sup>31</sup> These findings suggest that ischaemia/reperfusion injury may occur more frequently and/or to a greater extent in older patients attending for HBOT.

## HBOT and intraocular pressure

IOP in healthy subjects was measured during experimental exposure to normal atmospheric pressure and at double normal pressure (2 bar). IOP fell by a mean 1.25 mmHg during HBOT conditions.<sup>40</sup> IOP was reduced significantly by a mean 1.85 mmHg during HBOT (2.5 bar) treatment for a variety of indications.<sup>41</sup> That mean IOP was found to be reduced slightly in these studies<sup>40,41</sup> does not eliminate the possibility that IOP may have been elevated during HBOT in any individual subject without that finding influencing the statistical significance of the reported differences between the mean findings. It is not known if any glaucoma patients were included in these studies.<sup>40,41</sup> The global prevalence of glaucoma has been estimated to be 3.4% for ages 40–80, with POAG being more likely in people with African ancestry and primary closed angle glaucoma being more likely in people with Asian ancestry.<sup>42</sup>

## Hood versus mask administration of HBOT

Aqueous oxygen tension is mostly dependent on the systemic circulation of blood but also in part on the oxygen transmitted through the cornea from the atmosphere which was found to be the route for only 23.7% of the total.<sup>43</sup> It was concluded that oxygen levels in the anterior chamber angle are strongly influenced by oxygen derived from the ciliary body blood flow.<sup>44</sup> Accordingly, the partial pressure of oxygen in the posterior chamber was found to correlate strongly with the partial pressure at the anterior chamber angle.<sup>44</sup> Increased partial pressure of oxygen in the anterior chamber angle has the potential to damage trabecular meshwork cells.<sup>44</sup>

When HBOT is administered by oronasal mask the exposed corneal surface is only exposed to the normal concentrations of oxygen in air. Changes in aqueous humour oxygen level when HBOT involves administration by oronasal mask appears to be mainly dependent on oxygen derived from blood circulation. HBOT involving administration by hood



directly exposes the anterior corneal surface to increased oxygen concentrations which may contribute to increased aqueous humour oxygen levels (in addition to increases due to the ciliary body blood circulation). The myopic shift in response to HBOT was found to be significantly more pronounced when oxygen is delivered by hood compared to oronasal mask delivery.<sup>45</sup> When HBOT is indicated, oronasal mask administration may be advisable for patients who are susceptible to glaucomatous pathology.

## Neuroprotection

The multiple pathways leading to RGC degeneration following optic nerve injury has stimulated interest in the development of neuroprotective therapies which might be applicable to glaucoma.<sup>2</sup> Neuroprotection involves mechanisms within the nervous system which protect neurons from apoptosis or degeneration,<sup>3</sup> or, more optimistically, reversing the process of cell death.<sup>46</sup> Given the central role of mitochondria as both a source and target of oxidative stress, plus the growing implication of mitochondrial dysfunction in the pathogenesis of glaucoma, therapeutic approaches that target mitochondria may provide a means of protecting retinal ganglion or trabecular meshwork cells from glaucomatous degeneration.<sup>39</sup>

There has been increasing evidence that glaucomatous neurodegeneration is analogous to other neurodegenerative diseases in the central nervous system such as Alzheimer's disease.<sup>47</sup> To the extent that oxidative stress may reach pathological levels which are above the cell's antioxidant capacity, dietary antioxidant supplements such as Vitamin E and compound extract Ginko biloba may be of benefit in protecting RGCs.<sup>47</sup> Unfortunately, clinical trials for neuroprotective agents in glaucoma are restricted by the currently recognised end points for such trials (IOP and visual field evaluations) which do not permit swift and reliable assessment of neuroprotective outcomes.<sup>47</sup> Animal studies are an alternative approach. For example, a mouse model study supported the role of oxidative stress-related mechanisms of neuro-inflammation in experimental glaucoma as well as the potential for antioxidant treatment as an immunomodulation strategy for neuroprotection in glaucoma.<sup>48</sup>

## Discussion

Local and temporally limited disturbances of perfusion have been postulated as a potential source of trouble in patients with glaucoma.<sup>49</sup> Such vascular dysregulation, rather than leading to chronic hypoxaemia, may provoke reperfusion damage, either manifesting over time in the local damage observed in glaucoma, or promoting damage induced by other mechanisms such as high or unduly variable intraocular pressure.<sup>49</sup> The spectrum of potential ON damaging factors in glaucoma ranges from elevated IOP at one end to ischaemic and other factors at the other end.<sup>10</sup> However, elevated IOP and ischaemic mechanisms may be combined directly if intraneural ischaemia results from the IOP mechanical stress loading on the ON blood supply.<sup>5</sup> Thus, IOP and ocular blood flow probably act in concert.<sup>49</sup> There is good evidence that oxidative stress occurs in glaucoma and that it contributes to RGC<sup>39</sup> and/or trabecular

meshwork cell loss.<sup>29</sup> Mitochondrial dysfunction is central to these processes as both a cause and consequence of oxidative stress.<sup>39</sup> For example, a review found increasing evidence indicating that glutamate excitotoxicity and oxidative stress are associated with mitochondrial DNA alteration or DNA oxidation-related mitochondrial dysfunction in retinal neurodegeneration, including glaucoma.<sup>50</sup> Although neurons are prone to build up oxidative stress, as implicated in many neurodegenerative diseases, there is also an age-related component of oxidative stress due to the intrinsic ability of cells to respond to oxidative damage declining with age.<sup>7</sup> Age-related glaucoma progression would tend to undermine therapeutic strategies which may need to be intensified as ageing progresses. Oxidative stress, nutritional status and nutraceutical supplements have to be considered within the standards of care of older ophthalmological patients in relation to diseases such as glaucoma, dry eye, diabetic retinopathy and age-related macular degeneration.<sup>51</sup> as well as keratoconus, for example.<sup>38,52</sup> Neuroprotection in the field of glaucoma is defined as any treatment, independent of IOP reduction, which prevents RGC death.<sup>53</sup> The role of day-to-day episodes of IOP elevation such as those associated with postural changes, muscular effort, eye wiping or rubbing for example, in causing IOP fluctuation and associated reperfusion injury is yet to be established. For example, because light eye touching approximately doubles IOP and eye rubbing forces can elevate IOP by 100's of mmHg, there may be significant vascular and mechanical consequences from such episodes which are unrelated to reperfusion injury<sup>15</sup> as well as those which could be associated with reperfusion injury and oxidative stress. Episodes of intracranial pressure variation, in concert with or separate from IOP variations also have the potential to contribute to adverse mechanical and vascular consequences<sup>6</sup> which may also involve reperfusion injury and oxidative stress.

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