EXTREME ENVRONMENTS

The Eye in Extreme Environments

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What is the topic of this review?

The effect of extreme environments on the visual system.

What advances does it highlight?

The manner in which environmental stressors directly and indirectly affect the eye and vision.

Abstract

Much is known about the physiology and anatomy of the eye. Much less is known about the impact of different environments on the eye, and yet it is the pathophysiology that results from this interaction that is often the precursor to disaster. The present review focuses on the effect of different extreme environments on the visual system: in particular, the manner in which such environments affect the sensory mechanism of that system.

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Introduction

That the environments we explore, work and compete in are, for humans, best defined and relayed visually was acknowledged by Leonardo da Vinci in 1512:

"The eye, which is called the window of the soul, is the chief means whereby the understanding may most fully and abundantly appreciate the infinite works of nature"

The year 2019 marked the 500th anniversary of the death of Leonardo Da Vinci, a prolific student of the human body, who was the first to provide a detailed anatomical description of the vision system, with an accompanying treatise on the manner in which images are perceived. Although some of his deliberations on vision have not survived the test of time, his detailed artistry on the components of the visual apparatus are considered masterpieces.

Deliberations regarding the physics of the optics and physiology of vision have been intertwined throughout history. Scholars investigating the concept of light inadvertently also addressed the issue of how humans perceive light. Milestones include the description of the properties of light (reflection, refraction and colour), and of binocular vision by Ptolemy (in his treatise "Optics" written in the 1st century) and the resolution of whether vision was a function of emission (of light from the eyes, as suggested by Plato, Ptolemy, Galen etc.) or intromission (of light entering the eyes) by Ibn al-Haythan (Alhazen in Latin). In his "Book of Optics" (Kitab al-Manzir, printed in the 11th century) Ibn al-Haythan also proposed that the process of vision most likely occurs in the brain (Adamson 2016). Later, having become familiar with the principle of the *camera obscura* Kepler (1604) suggested that due to the eye's lens, images are projected onto the retina inverted and reversed, and subsequently corrected in the brain.

Since the Renaissance, humans have visited nearly all environments on our planet, and current efforts have resulted in our permanent presence in lower Earth orbit (International Space Station, ISS), with the likelihood of settlements being established on the Moon and Mars within this century. In this, as well as many other extreme environments, questions remain to be resolved about the effect of different environments and their combination on the visual system.

In this review we examine the impact of a range of extreme environments (wind, low humidity, ultraviolet radiation, submersion, hyper- and hypobaric, temperature, hyper- and microgravity, confinement) on the structure and function of the eye and visual system and, where appropriate, ways of mitigating problems. In so doing we examine the link between

environmental stressors and the anatomy, physiology and pathophysiology of the eye. The importance of this area is founded in the eye being the primary source of sensory information for humans, and the impairment of vision often being the precursor to disaster in extreme environments.

Anatomical & Physiological considerations

The visual sensory system includes the sensory organs (eyes), optic nerves, optic chiasma, optic tract, lateral geniculate nucleus in the thalamus and the visual cortex (Glaser 1993). Extreme environments can have detrimental impacts on different parts of this system.

As is common with other tissues, there is a strong link between the structure and function of the visual sensory system, and its consequent susceptibility to damage and functional impairment in extreme environments. For example, the eye is located in the orbit, a protective and supportive bone structure in the skull in which the eye is surrounded by: extra-ocular muscles that control movement of the eye; several intracranial nerves; blood vessels; and orbital fat tissue. This provides mechanical protection and insulation of the eyeball (Sherman and Lemke 1993). Also eyebrows, eyelashes and repetitive blinking of the eyelids create a defence against the direct effect of environmental factors. The eye surface (cornea and conjunctiva) is innervated by polymodal nociceptor neurons whose nerve endings are tonically activated by mechanical forces, and also respond to temperature (Belmonte and Gallar 2011; Belmonte *et al.* 2004). Injured or inflamed tissues are the origin of spontaneous sensations of stinging and burning pain. These sensations on the ocular surface elicit reflex motor and autonomic responses of blinking, tearing and conjunctival vasodilatation, and possibly blepharospasm, aimed to protect the eye from further injury (Belmonte *et al.* 2015).

The eye has a dual vascular supply: uveal and retinal. The very rich vascularisation and high blood flow of the uvea ensures that the eye normally has a stable temperature. In the retina, efficient autoregulatory mechanisms prevent changes in retinal blood flow over a wide range of perfusion pressures (Robinson *et al.* 1986). Finally, the eye is filled with the non-compressible aqueous and vitreous humours, thus changes in ambient pressure, such as reduced pressure at high altitude and increased pressure in a deep-sea environment, do not have a direct, clinically significant, influence on the eye.

Environmental factors can affect both the optical and (neuro-) physiological components of the vision system, in a *direct* and *indirect* manner, respectively. As a result of its structure, only a small part of the eye, the anterior part in the interpalpebral aperture, is in direct contact with the environment and the direct effects of environmental factors pertain primarily to this region, which is responsible for adequate refraction of light. The light passes through a thin layer of tear film, the cornea, aqueous humour in the anterior chamber, the crystalline lens and vitreous humour, with each of these structures possessing different refractive characteristics. To be able to perceive a sharp image, the light that enters the eye must be focused on the macula, which is the central part of the retina, a photosensitive layer of the posterior part of the eye (Figure 1). To maintain refractive function, the cornea, lens and liquids in the eye must be transparent. Any environmental factors that affect the tear film and corneal layer, and consequently the refraction of light through these layers, distort the image projected on the retina and impair vision. Such environmental factors include dry and windy air, high levels of UV radiation and submersion.

By far the most significant acute effects on the structures of the eye, and thus potentially on vision, are the indirect effects of the environment on eye structures and function, primarily resulting in a decreased oxygen delivery to the retina and central nervous system, as a consequence of reduced blood supply. Such perfusion-limited oxygen delivery can also be due to the increased head-to-foot gravitational vector, which decreases perfusion of the brain and can cause “grey-out” and “black-out”. Oxygen delivery can also be diffusion limited, as occurs during exposure to lower partial pressures of oxygen at altitude. Rapid decreases in ambient pressure cause inert gas dissolved in the tissues of the eye to form a gas phase and influence sight. Whereas the influences of elevated gravitation forces on vision via an influence on the systemic circulation are well known (for review see Rainford and Gradwell, 2006), the mechanisms and consequences of reduced Gz-force on the structures of the eye are not yet understood.

In the sections that follow we focus on the environment-related direct and indirect factors that impact upon vision.

Wind and low humidity

Wind and low humidity mainly affect the exposed ocular surface between the eyelids. The cornea and conjunctiva are covered by tear film; the outermost layer of the tear film is the

primary refracting surface for light entering the visual system. The tear film is also responsible for lubrication of the cornea and thus ocular comfort, nourishment and protection of the ocular surface. It is composed of three layers: mucin, aqueous and lipid. The efficacy of the functions of the cornea rely on the integrity and thickness of all three layers. Tear film disruption can lead to ocular surface damage and blurred vision (Willcox *et al.* 2017).

Dry environments, as experienced at altitude or in air-conditioned airplane cabins (Uciyama 2007), increase aqueous tear film evaporation, decrease lipid layer thickness, reduce tear production and provoke destabilization of tear film despite sufficient tear production (Willcox *et al.* 2017, Abusharha & Pearce 2013). At high altitude, the dry atmosphere is combined with the stressors of wind, cold and ultraviolet radiation, reducing the amount and/or alteration of the composition of lubricating tear film coating the ocular surface (Willmann *et al.* 2014). Although wind, dryness, and extreme environmental temperatures elicit conscious sensations and the reflex response of blinking and lacrimation, these responses are sometimes not sufficient to protect the eye from further injury and result in dry eye symptoms, which may lead to serious eye health problems (Clayton 2018).

Symptoms of "dry eye" are the sensation of a foreign body and burning in the eye, light sensitivity, blurred vision and redness of eyes. Dry eye syndrome is exacerbated in individuals with pre-existing dry eye (Willmann *et al.* 2014), or having refractive eye surgery. Dry eye symptoms are, therefore, common in environments such as high altitude, desert and air-conditioned (cooled) artificial environments (*i.e.* the International Space Station, ISS).

Topical tear substitutes and lubricating ointment without preservatives can relieve symptoms of eye discomfort for most people. The substitutes should be applied frequently (6-8 times per day); however, their use during high wind and extreme cold can be problematic. High-viscosity lubricants used at bedtime can help healing during sleep. Properly fitted goggles that protect the eye from wind and UV light can help by increasing the moisture in the microclimate around the eye surface.

Ultraviolet radiation

Damage to the eyes, or rather vision, was frequently reported by early solar observers either discovering sunspots (*i.e.* Galileo Galilei and Thomas Harriot), trying to measure the diameter of

the sun (*i.e.* John Greaves), or investigating the spectrum of after-images of the sun (*i.e.* Isaac Newton).

The human eye is constantly exposed to low levels of solar ultraviolet (UV) radiation without any negative consequence. However, high doses of UV radiation can cause damage. UV radiation is invisible to human perception. It represents the shortwave electromagnetic spectrum of 100-400 nm and is divided into UV-A, UV-B and UV-C. Extremely short and high energy UV-C rays are almost completely absorbed by the ozone layer. A high fraction of UV-B rays reaching the eye are absorbed by the cornea, particularly the corneal epithelium, and only a small proportion reach the intraocular lens. As a result, UV-B radiation may cause keratitis. UV-A radiation penetrates deeper into the eye, and may cause solar maculopathy during acute exposures, and cataract formation as a result of chronic exposure. Direct sunlight contributes only about 50 % of ambient UV radiation; the rest is scattered and ground reflected UV radiation (International Commission on Non-Ionizing Radiation Protection, 2010)

When the threshold radiation dose of UV irradiation for biological damage is reached, absorption of UV radiation leads to oxidative photodegradation. In the corneal epithelium, the proposed mechanism of UV-induced phototoxicity involves a combination of: oxidative stress from reactive oxygen species formation; inflammation induced by upregulation of proinflammatory cytokines; and apoptotic cell death through necrotic receptor activation (Willmann 2015). UV irradiation-induced damage of the cornea is known as ultraviolet keratitis or photokeratitis. High mountain regions with snow-covered areas are particularly dangerous for UV-induced damage of the cornea, as solar UV radiation increases with altitude, and snow reflects more than 90 % of UV rays. Under such conditions UV keratitis is particularly frequent, and commonly known as “snow blindness”.

UV keratitis usually presents with severe ocular pain and tearing, which leads to uncontrolled blinking of the eyelid and blepharospasm. The conjunctiva becomes increasingly red and can become edematous. Both eyes are affected. The onset of ocular pain, which can sometimes be very strong, is typically delayed several hours after exposure.

Due to the fast re-epithelisation of the cornea, symptoms usually resolve within 1-3 days, depending on the degree of UV damage. Clinical symptoms of UV keratitis can be diminished by frequent use of topical lubrication, and in moderate to severe cases by administering a bandage contact lens; topical antibiotic ointment are sometimes suggested to prevent infection of

damaged cornea. Occasionally systemic analgesics are needed to relieve the pain. Topical anesthetics, although they stop the eye pain and constant blinking, are not recommended, because they delay corneal re-epithelisation. However, in emergency situations, such as the need to descend from altitude safely, short-term application may be considered (Willmann 2015).

Exposure to UV over long periods can result in more serious damage to the eye, like pterygium and cataract. Pterygium is abnormal growth of the conjunctiva onto the cornea, which can cause ocular irritation and, in the late stage of the corneal tissue's invasion, visual impairment (Wlodarczyk *et al.* 2001). There is also strong association between solar radiation exposure and incidence of cataracts, which reduce vision, and without surgery lead to severe visual impairment (Lucas *et al.* 2006, Modenese *at al.* 2018, Oriowo *et al.* 2001).

Solar maculopathy is an occurrence not only among "sun gazers", but also among individuals exposed to sunlight at altitude. The retina absorbs on average from 10^{12} to 10^{15} photons daily (Hunter *et al.* 2012) without any detrimental effect. However, at a certain level, the bombardment of the retina by photons will cause photochemical damage which, depending on the severity and location of the damage, is reversible or irreversible. The inner retinal cells (*i.e.* ganglion cells, Müller cells, amacrine cells, and bipolar cells) are mostly transparent and resilient to photoxicity (Hunter *et al.* 2012), whereas rods and cones, which need to absorb photons as the first step of the "seeing" process, are most susceptible to photochemical damage. Solar maculopathy can result from a single or repeated unprotected exposures to bright sunlight, and the degree of photochemical damage depends on the intensity and duration of the exposure, with younger individuals being more susceptible (Abdellah *et al*. 2019). In most cases, mean best corrected visual activity (mean BCVA) returns towards normal values within 6 months (Abdellah *et al.* 2019), despite persistent disruption of outer retina layers.

Ocular exposure to UV radiation can be substantially reduced by a variety of measures. The hand salute, for example, supposedly stems from the tradition of soldiers in Ancient Greece shielding their eyes. At present, effective measures include personal protection, such as wearing a hat with a wide brim and use of UV-blocking sunglasses with side shields. UV-blocking soft contact lenses that completely cover the cornea are also a good option (Chandler 2011). The use of artificial tears, especially in environments or conditions where tear film stability is reduced, can also add to prevention.

Underwater environment

The underwater environment presents several stressors to the eyes: water (either sea or fresh), elevated pressure, and (usually) low temperatures. Natural (sea and fresh) water contain a variety of particulate matter, and their optical properties vary accordingly. The following discussion will focus on general characteristics of water, and how these influence vision.

When light travels through water, the amount of available light decreases with increasing depth due to absorption and scattering. Thus, at 200 metres of sea water there is negligible light available. It is not only the intensity of light that diminishes with depth, but also the available light spectrum. Different wavelengths of light are selectively absorbed, such that longer wavelengths (*i.e.* red and yellow) are absorbed first, whereas shorter wavelengths penetrate further (*i.e.* blue and green). As a consequence, red usually disappears at around 10 metres of sea water (msw) and yellow is not seen below 25 msw. At depths greater than 30 msw objects appear bluish-grey. With increasing depth, artificial lighting is essential for determining the colour of any object. Although sea water is an effective filter for UV wavelengths, the comments above regarding UV light also apply to shallow depths in clear water; shorter wavelength UV light penetrates to nearly 10 m (Somers, 1990).

Light is refracted at any interface of two media. Thus, in an air environment, a light beam travelling from the surrounding air environment through the tissue and fluid filled compartments of the eye will undergo several refractions prior to reaching the retina. At each refractive interface the image is subject to distortion. The structure and function of the eye has evolved to account for these refractions at boundaries occurring at the corneal layers, anterior chamber, lens, posterior chamber (vitreous fluid), such that in an eye under normal environmental conditions, the image projected onto the retina is in focus. An image observed underwater (without eye protection) appears out of focus (blurred) due to the significant change in refraction that occurs at the boundary between the water and corneal layers. In air, most of the light refraction in the eye (about 80 %) takes place at the first surface, *i.e.* on the cornea. The transition from air into the cornea is the largest change in index of refraction encountered by light entering the eye. Refraction also takes place in the converging lens of the eye, but its refractive power is not as strong as the cornea and contributes to fine tuning the image on the retina. During submersion, the air-cornea interface becomes a water-cornea

interface. The index of refraction from water to cornea is much lower and the refractive power of the eye is very much reduced, resulting in hyperopia and blurring of underwater vision (Butler 1995).

The problem of diminishing light intensity and colour perception with depth can be remedied with artificial lighting, whereas the air-cornea interface can be restored simply by wearing a facemask, thus eliminating the water-induced hyperopia. Due to the refraction of the light between the water and facemask glass, an observed object underwater appears to be magnified by about 30 %.

Hyperbaric environment

Another consequence of the underwater environment is increasing ambient pressure. This can also be achieved when exposing humans to elevated pressure in a hyperbaric chamber. Regardless of whether the surrounding pressure is increased in a water or air medium, it will not affect the size or shape of the eye, since the eye is filled with (incompressible) fluid. The elevation in ambient pressure has as a consequence the increase in the partial pressures of the constituent gases, such that a hyperbaric air environment (compressed air diving) will have an elevated partial pressure of oxygen and nitrogen (the inert gas component of air). In saturation diving, normally conducted at greater depths than with compressed air diving, the nitrogen (inert gas) component of air is substituted with helium.

In diving, with increasing pressure gas volumes are reduced (Boyle's Law). The face mask of a diver represents such a volume. Ineffective equalization of the pressure within the face mask (*i.e.* not introducing air into the mask volume by exhaling through the nose) may result in ocular barotrauma. When a face mask is used for diving, the air-filled space in the mask is subject to compression during the dive, due to increased ambient pressure. During descent, a relative negative pressure develops in this space, if the diver does not expel gas through the nose into the mask. This can result in drawing the eyes and ocular adnexae towards this space resulting in tissue and blood vessel disruption. Ocular barotrauma is presented with marked oedema of the eyelids, skin haemorrhages (ecchymosis) around the eyes, and subconjunctival haemorrhages (Barreiros *et al.* 2017). These changes may have a very dramatic outward appearance, but they typically resolve over several days without specific treatment and with no permanent consequences.

Barotrauma can also occur within tissues due to inappropriate decompression procedures. Namely, during the compression phase of a dive, the inert gas component is absorbed by body tissues according to the Haldane theory of inert gas exchange (Haldane *et al.* 1908); the amount absorbed being dependent on the gradients between the partial pressures of the inert gas in the breathing mixture (determined by the depth of the dive) and tissues, and the duration of the dive. The amount of gas that will dissolve in a tissue at a given temperature is directly proportional to the partial pressure of that gas (Henry's Law). During a dive (hyperbaric exposure) an inappropriately rapid reduction in ambient pressure on ascent will result in the inert gas dissolved in the tissues transforming into a gas phase (Somers 1990). As a consequence, inert gas bubbles form in the tissues, and the severity of the problem this causes is dependent on the location of the bubbles. These bubbles may result in clinical signs and symptoms; the condition is called decompression sickness (Francis & Mitchell 2004). Another disorder in which dysbaric intravascular bubble formation may occur is arterial gas embolism. Due to a rapid decrease of ambient pressure on ascent from depth, gas expansion inside the alveoli of lungs may result in alveolar rupture (Boyle's Law). Gas bubbles that are formed then enter the systemic circulation and can disrupt blood flow, in general, and blood flow to the eye, in particular (Neuman 2004).

The incidence and severity of decompression sickness depends on the nature of the decompression, specifically whether it is a decompression conducted during diving (*i.e.* underwater), or whether it is due to sudden exposure to a hypobaric air environment (*i.e.* decompression of an airplane cabin or fast ascent to high altitude).

Most ocular symptoms in patients with decompression sickness are due to ischemic trauma to the brain and neural tissue so they mainly occur with other neurological symptoms or findings. Ocular manifestations include nystagmus, visual field defects and optic neuropathy. Microemboli of gas in the systemic circulation can also cause central retinal artery occlusion resulting in sudden severe loss of vision of the affected eye and poor prognosis; at present there is no effective therapy. Smaller bubbles may provoke more located retinal and choroidal ischaemic injuries that usually do not affect vision (Hsu *et al.* 1992, Fodor *et al.* 2007).

During compressed air diving, the partial pressures of inspired oxygen and nitrogen increase with depth. Whereas the inspired partial pressures of oxygen (PO_2) and nitrogen (PN_2) at the surface (barometric pressure 1ATA) will be 0.2 ATA (20 %) and 0.8 ATA (80 %), respectively, at a depth of 40 msw (5 ATA), the partial pressure of oxygen will be 1.0 ATA, and that of

nitrogen 4.0 ATA. Thus, breathing an air mixture at 50 msw is analogous to breathing pure oxygen at the surface. Divers are therefore exposed to hyperoxia during air dives. A case report has been presented by Butler *et al.* (1999), indicating that hyperoxia may be implicated in the myopia observed in a diver. During the course of 18 days, a diver conducted dives using a nitrogen-oxygen breathing mixtures, inspiring a partial pressure of oxygen of 1.3 ATA for an average of 4 h each day. Breathing a hyperoxic mixture is known to increase the risk of pulmonary and/or central nervous system oxygen toxicity. The symptoms of the former are irritation of the respiratory tract, whereas the latter may manifest as seizures. Hyperoxic exposure can cause an increase in refractive power of the lens. This can manifest as blurred vision due to hyperoxic myopia, which vanishes gradually after termination of the hyperoxic exposure (Anderson & Farmer 1978).

Adherence to published decompression tables reduces the risk of diving decompression sickness, and adequate aircraft pressurization does the same for altitude decompression sickness. Treatment of decompression sickness is recompression in a hyperbaric chamber, followed by a gradual and staged decompression according to relevant decompression treatment guidelines, which also specify the frequency and duration of hyperbaric oxygen breathing.

Hypobaric environment

With the invention of the vacuum pump, Boyle (New experiments, 1660) explored the relation between the change in pressure and volume (Boyle's Law), at a constant temperature (this was added by Mariotte, and consequently the law is also referred to as Boyle-Mariotte's Law). On one occasion placing a viper in such a chamber and following exposure of the viper to a sudden and significant decrease in ambient pressure, Boyle reported observing bubbles evolving in the eyes of the snake. This anecdotal observation was relatively ignored, until bubbles were observed in the tear film of subjects either decompressed from a high-pressure environment to sea level (Mekjavic *et al.* 1998, Jaki & Mekjavic 2007), or from sea level to altitude (Strath *et al.* 1992). These decompression-induced bubbles appear at the interface between the eyelid and cornea, and therefore do not affect vision. These tear film bubbles may be an index of decompression severity for recreational dives (*i.e.* shallow and short in duration). Interestingly, their occurrence persists for more than 24 hrs after the dive (Mekjavic *et al.* 1998, Jaki &

Mekjavic 2007), suggesting continued post-decompression elimination of inert gas during this time.

In low-pressure environments, the partial pressure of oxygen (PO_2) is reduced, resulting in a lower alveolar PO_2 and consequently lower arterial and tissue PO_2. During exposure to hypoxia, the most affected tissues in the eye are the cornea and retina. Hypobaria results in an increase in corneal thickness due to swelling of the central layer of the cornea, the corneal stroma. This is most likely due to hypoxia-induced endothelial pump deficit (Bonnano 2001). It has been shown that changes in systemic PO_2 parallel those of increased corneal thickness. Due to hypobaria, the cornea thickens uniformly and does not affect corneal clarity, and the swelling of stroma does not appear to affect vision (Bosch *et al*. 2010). The increase in corneal thickness is reversible. Hypoxia affects vision in corneas that have preexisting anatomical abnormalities, such as low endothelial cell counts or surgical alterations, such as keratorefractive surgery (Winkle *et al.* 1998, Nelson *et al.* 2001). In cases where the oedema spreads anteriorly from stroma into the corneal epithelium, pain and profound vision loss can occur.

Many individuals with refractive errors find glasses or contact lenses ill-suited to extreme environments (Josephson & Caffery 1991). During exertion, poorly designed glasses will allow the moisture of expired air to condense on the glasses (*i.e.* fogging), coupled with the snow, resulting in obscured vision. Substituting glasses with contact lenses may not always be optimal. Proper daily use and hygiene maintenance of contact lenses may be very difficult in extreme environments, but is obligatory in order to avoid painful and vision-threatening infection of the cornea.

Currently, keratorefractive surgery is a popular procedure to eliminate the need for eyewear. In the past, radial keratotomy (RK) with corneal incisions, not including the central part, was widely used to correct myopia. RK resulted in steepening of the peripheral and flattening of the central cornea, thus improving distant vision. Normal vision at sea level can result in problems with near vision at altitude in patients after RK. Several studies have reported significant visual decrements after 24 hours of exposure to altitude (Mader & White 1995, 2012). The most likely aetiology is hypoxia-induced corneal contour changes that lead to new refractive error, *i.e.* hyperopic shift. At present, RK has been largely replaced with newer, laser keratorefractive techniques such as photorefractive keratectomy (PRK), laser sub-epithelial keratomileusis (LASEK), laser-assisted *in situ* keratomileusis (LASIK), and small incision lenticule extraction (SMILE). These procedures reshape the anterior part of the cornea and do not directly affect the deeper stroma. Corneal oedema, induced by hypoxia in such corneas, is more uniform across the

area, and the shape of the anterior corneal surface remains unchanged. Thus, visual acuity in laser kertatorefractive patients is much less affected in hypoxia than it is in RK patients. It also appears that the magnitude of the hyperopic or myopic shift diminishes with increased postoperative time (Nelson *et al.* 2001).

The nervous system comprises 2 % of body mass, but accounts for 20 % of the total resting oxygen uptake (Barbur & Connolly 2011), with the retina consuming more oxygen per unit mass than the brain. This demonstrates the importance of adequate retinal oxygenation to maintain visual function. Hypoxia causes a reduction in the dark adaptation, gradual loss of peripheral vision (Ernest & Krill 1971), and changes in the sensitivity to colour (Barbur & Connolly 2011).

Lower arterial oxygen saturation also causes an increase in the diameter of the retinal arterioles and venules to maintain retinal blood flow (Louwies *et al.* 2016). Appropriate perfusion of the brain and retina is achieved by autoregulatory mechanisms, which have evolved to meet the metabolic demands of these tissues. When oxygen supply is reduced due to decreased tissue PO_2, retinal vessels become tortuous and dilated, thus augmenting blood flow. Also, retinal haemorrhages are often observed in the hypoxic environments of altitude, probably due to hypoxia-induced capillary fragility (Hunter *et al.* 1986) and endothelial dysfunction of retinal vessels (Sousa *et al.* 2018).

The most common hypobaric hypoxic exposures during recreational activities occur during skiing and mountaineering, where the effect of altitude-related hypoxia on the eye is combined with stresses of UV irradiation, cold and wind. Acute exposure to altitude initiates physiological adjustments to improve hypoxic tolerance. Prolonged exposures result in acclimatization to altitude and reduce the negative sight-related effects of hypoxia. Indeed, hypoxia-induced eye changes are less evident as acclimatization progresses (Bosch *et al.* 2010). A survey of vitreo-retinal disorders of Sherpas living at high altitude in Nepal reported that high altitude retinopathy without, and with, dry age-related macular degeneration accounted for 16 % and 3.7 % of vitreo-retinal disorders in a population of 81 patients, respectively (Thapa *et al.* 2013). Solar retinopathy accounted for only 2.5 % of the disorders.

The frequent high altitude-related changes of the retina are commonly known as high altitude retinopathy (HAR), and may be the result of a combined effect of systemic hypoxia and increased blood viscosity (Barthelmes *et al.* 2011, Wiedeman & Tabin 1999). HAR-related changes can include: increasingly dilated retinal veins and arteries; haemorrhaging in the inner retina and pre-retinal space; optic disc hyperaemia; optic disc swelling; and haemorrhages in

the vitreous cavity (Fig. 2). Valsalva manoeuvres associated with extreme effort, as in climbing or extreme skiing, can also contribute to retinal and pre-retinal haemorrhaging (Brinchmann-Hansen *et al.* 1989, Jaki Mekjavic *et al.* 2002). It remains unresolved, whether HAR could be considered a warning sign of impending high altitude cerebral oedema, the end stage of acute mountain sickness (Bosch *et al.* 2009, Barthelmes *et al.* 2011; Willmann *et al.* 2011).

All changes observed in HAR may go unnoticed and disappear within days or weeks after descent. On the other hand, when haemorrhages are located in the central part of the retina, the fovea, or in the case of spill-over of blood into the vitreous humour, severe visual impairment may result. HAR usually affects both eyes, but may affect vision in one eye only, which significantly influences safety due to sudden loss of depth perception. In such cases, descent should proceed with care and assistance. HAR changes resolve over days or weeks, and occasionally the detrimental effect on vision can be irreversible (McFadden *et al.* 1981).

Extremes of temperature

Temperature-related injury of the eye is not often reported in the literature; this may be because of good anatomical and functional protection against temperature impacts on the eye. It has been proposed that the temperature of the eye is maintained by the very high choroidal blood flow. Choroidal blood vessels are innervated by trigeminal sensory fibers that also appear to affect choroidal blood flow in response to temperature increases or decreases (Reiner *et al.* 2012). The surface of the eye is innervated by trigeminal neurons, the peripheral nerve endings of which detect, among other things, thermal stimuli, and elicit reflex blinking, dilatation of vessels in the conjunctiva and lacrimation (Belmonte & Gallar 2011). This response results in warming and renewing the protection offered by tear film. Despite this, after prolonged exposure to intense cold the corneal surface can become insensitive to thermal or mechanical stimuli. This was first reported in the case of an airman officer who, in 1917, experienced the loss of his protecting spectacles during an aerial expedition at an altitude of 4500 m over snow covered mountains with a temperature of about -25 °C. This resulted in a lesion in the cornea which was described as “ground glass opacity, most marked in the centre” and epithelial desquamation (Colombo 1921). Transient eye problems were reported in a case of an ultra-marathon runner exposed to high wind speed and sub-zero temperatures. After reporting decreased visual acuity, ‘cloudy’ vision, the sensation of having a foreign body in the eye and observing generalized edema of cornea, the diagnose freezing of cornea was made (Cope & Kropelnicki 2015). However, corneal edema can also be due to stromal lactate accumulation as a consequence of thermal stressors, enhanced glycolysis (Moshifar *et al.* 2018), or due to hypoxia

because of exercise-induced hypoxaemia (Winkle *et al.* 1998, Dempsey & Wagner 1999).

The effect of hot environments on the eye is mainly related to specific eye diseases prevalent in hot climates and resulting from infections, parasites and insect vectors, *i.e.* factors beyond the scope of this review. Epidemiological studies indicate a link between chronic exposure to high temperature environment and cataract formation (Al-Ghadyan 1986). Damage of the eye lens after exposure to heat has been reported in experimental condition *in vitro*. Bovine lenses were exposed to simulated thermal conditions within a bakery for different durations. The heat exposure caused optical damage to the lenses, which was recovered, but in some exposures (*i.e.* 1 hr at 39.5 °C) the damage to the epithelial cells remained (Sharon *et al.* 2008).

Hyper- and microgravity

On Earth, the human body is constantly exposed to the force of gravity (9.8 $m.s^{-2}$), thus the structure and function of all physiological systems have evolved under this environmental stressor. With the development of high performance aircraft, humans can be exposed to transient changes in gravitation loading, which affect the cardiovascular system and, indirectly, vision (Lee *et al.* 2018). In contrast, humans have established a permanent presence in lower orbit on the ISS, and much research has been conducted to understand the adaptation of physiological systems to microgravity, or rather to implement countermeasures to minimize the debilitating impacts of this adaptation (Mekjavic *et al.* 2020). Recent observations of visual impairment in astronauts (Mader *et al.* 2011) have rendered the unresolved effect of microgravity on the visual apparatus a high priority in Space Life Sciences research.

While acceleration is a vector quantity, g-force accelerations are often expressed as scalar, with positive g-forces pointing downward in the head-to foot direction (indicating upward acceleration), and negative g-forces pointing upward (foot-to head direction). Positive g-force is thus experienced in acceleration upward and, if excessive and sustained, it drains blood away from brain toward the legs, causing a drop in arterial blood pressure in the head and also a drop in the pressure in the ophthalmic artery that supplies the eye.

When a point is reached where the arterial pressure in the ophthalmic artery no longer exceeds the intraocular pressure, retinal perfusion is reduced. Since the retinal tissue has the highest rate of oxygen consumption in the body (Barbur & Connolly 2011), it is very sensitive to changes in perfusion and responds to ischaemia with visual alterations. Retinal hypoxia results

in loss of colour vision, vision becomes dim: a condition called "grey-out", and is an early sign of hypoxia in this situation. Continued loss of perfusion causes loss of peripheral vision, with only central vision being retained. This is commonly referred to as tunnel vision and can lead to total loss of vision, or "black-out", if the increased head-to-foot gravitational vector is maintained. These rapid changes of visual function and perception normally precede gravitational-induced loss of consciousness (G-LOC) due to cerebral hypoxia. This loss of vision is reversible with complete recovery of visual field following normalization of the g-force.

Assuming that an individual is in the upright position, a downward acceleration faster than the rate of natural free-fall, will induce a negative g-force. If the negative g-force is sufficient to redistribute blood from the lower part of the body to the head, this will result in congestion of blood vessels of the upper part of the body. Visually, a so called "red-out" may occur, which may be due to looking through a congested lower eyelid coming into the visual field due to the negative-g. It is potentially dangerous causing retinal haemorrhages and haemorrhagic stroke.

The effect of positive g-force can be prevented, to some degree, by practicing the straining maneuver, positive pressure breathing, and wearing an anti-G-suit. There is no effective countermeasure available for negative g-force.

Prolonged sojourns in a reduced gravity environment induce mechanisms of adaptation to microgravity, which include loss of body mass (specifically lean muscle and bone tissue), decreased sensory inputs within the body as well as redistribution of fluids from the lower to the upper body (Hargens & Richardson 2009). In the last decade, some specific changes in the morphology and function of the eye have been documented in astronauts after long duration space flight; these include visual performance decrements and one or more ocular findings, *e.g.* hyperopic shift, cotton-wool spots, choroidal folds, optic disc edema, optic nerve sheath distention, and posterior globe flattening with varying degrees of severity and performance (Mader *et al.* 2011). These changes have been defined as the Spaceflight Associated Neuro-ocular Syndrome (SANS). SANS can potentially have a serious impact on space exploration; currently one of the major hurdles for human deep space exploration is the unresolved loss of vision as a consequence of prolonged exposure to the environment in the ISS . Few data exist from which the extent, cause and risk of SANS can be determined. Multifactorial pathogenesis is likely, including: cephalad fluid shift; change in intracranial pressure; alterations in cerebrospinal fluid dynamics; anatomic and genetic predisposition. Countermeasures to mitigate potential long-term sequelae are yet to be identified. Our recent studies suggest that

the daily exercise conducted by astronauts to mitigate musculoskeletal atrophy within the hypercapnic environment of the ISS causes significant elevations in intraocular pressure (ocular hypertension), which may contribute to the aetiology of SANS (Mekjavic *et al.* 2020).

A recent study by Ficarotta & Passaglia (2020) has introduced a new theory on the interaction of intracranial pressure with intraocular pressure (IOP), which has implications for our understanding of the potential aetiology of SANS. In a rodent model these authors varied the intracranial pressure (ICP) and monitored aqueous humor outflow. Their results suggest that increases in ICP instigate a neural feedback mechanism which decreases aqueous outflow, thus elevating IOP. In this manner the IOP balances the increases in ICP, thus preventing any alterations in the translaminar pressure gradient across the optic nerve which could result in optic nerve damage.

Confinement

In extreme environments, it is not unusual to expect individuals to be sequestered in habitats that protect them from the external environment and provide a comfortable living environment. Depending on the size of the living quarters, individuals may require a lesser or greater degree of visual accommodation (lens shape change), which could result in myopia. To investigate the IOP developed during accommodation, Young (1971) surgically implanted a pressure sensor in the vitreous chamber of monkeys, and monitored vitreous pressure during focusing effort (accommodation). He noted a 50 % increase (6mmHg) above normal in vitreous pressure during focusing effort, and concluded that myopia can result from a continuous level of visual accommodation. This was confirmed by a later study (Young & Leary 1973), in which the visual refractive characteristics of monkeys were compared based on the visual environment to which they were exposed. Specifically, a visual environment requiring more accommodation (*i.e.* cages) induced a higher risk of myopia. Interestingly, Young noted that myopia could be created by placing two animals together in a cage, which does not permit the animals to see at a distance, such that vision would rely on accommodation and convergence. Social interaction among primates includes near-point grooming behavior, which would tend to promote myopia.

The phenomenon of accommodation-induced myopia has also been reported in submariners (Schwartz & Sandberg 1954; Kinney *et al*. 1979), who live and work in a confined space. An additional problem with confined habitats is the often observed increase in ambient partial

pressure of carbon dioxide, due to the inefficiency of currently available carbon dioxide scrubbers. Recent evidence suggests that, whereas the choroidal circulation is affected by the hydrostatic factor (*i.e.* position of the head), the circulation in the retinal nerve fibre layer is influenced by hypercapnia (Jaki Mekjavic *et al.* 2016).

Confounding and contributing factors

As has been alluded to in previous sections, exposure to extreme environments often comprises exposure to more than one environmental factor. These factors may have synergistic or antagonistic effects. In addition to the physical environmental factors, a variety of other non-environmental factors will modify some of the responses reviewed. This is an area requiring further research. Of the many such factors, two are briefly addressed below, exercise and ageing.

Exposure to extreme environments is often accompanied by extraordinary physical exertion. The effect of physical exercise on IOP has been of interest since the 1960s, when it was observed that in contrast to the elevation in mean arterial pressure (MAP) IOP decreases. One of the earliest studies conducted by Cooper *et al.* (1965) was to determine the potential therapeutic effect of the post-exercise decrease in IOP in open-angle glaucoma patients. During aerobic exercise, the reduction in IOP is a function of the exercise modality (Myers 1974), intensity (Qureshi 1995) and duration (Ashkenazi *et al.* 1992), as well as an individual's fitness level (Passo *et al.* 1987). The mechanism by which exercise lowers IOP remains unresolved, but the factors implicated in this response are decreased blood pH, elevated plasma osmolarity, and elevated blood lactate (for review see Risner *et al.* 2009). In contrast to aerobic exercise, isometric exercise elevates IOP (Vieira *et al*. 2006), and the increase is proportional to the increase in systemic blood pressure (Bakke *et al.* 2009). Weight lifting, for example significantly increases IOP, which is further augmented by breath holding (Vieira *et al.* 2003, 2006). During isometric exercise, Robinson *et al.* (1986) have demonstrated that the retina efficiently autoregulates retinal blood flow during acute hypertension up to a mean brachial artery pressure of 115 mmHg. Thereafter, retinal blood flow increases proportionately with increases in mean brachial artery pressure. An example of the effect of an exertion in an extreme environment is shown in Fig. 3; this depicts the fundus photograph of an alpinist (Davo Karničar), who was the first to ski from the summit of Mt. Everest to Base Camp. Comparison of the pre- and post-expedition photographs reveal a hemorrhage (retinopathy) after the exertion

(*i.e.* Valsalva retinopathy).

Not surprisingly, exposure to extreme environments is usually the domain of younger adults. Thus, most of the published data of ophthalmological responses to exposures to extreme environments deal with healthy young male populations. The recent observations of the development of vision impairment in astronauts is a rare exception, since astronauts working on the International Space Station are middle-aged. Prior to the ISS, astronauts were younger, and were not required to conduct the levels of exercise seen today. A recent study (Mekjavic *et al.* 2020) has examined the IOP response to hand grip exercise in subjects aged 50 to 65. In contrast to a younger group (Mlinar *et al.* 2020, *unpublished*), their exercise-induced increase in IOP was much greater. It is speculated that the difference in the IOP response to static handgrip exercise might be the age-related change in the structure of the lamina cribrosa (Kotecha *et al.* 2006), or an age-related change in the ICP-dependent neural feedback mechanism protecting the optic nerve from damage by maintaining the translaminar pressure gradient (Ficarotta & Passaglia, 2020).

Exposure to extreme environments is no longer the domain of physically trained young adults. Ascent to Mt. Everest is now achieved by older individuals. In Europe, families can safely access 450 resorts located at altitudes above 2000 metres. Of these over 50 are located at altitudes at, or above, 3000 metres. Little information is available on the effects of hypoxia at such altitudes on eye health of older adults and children.

Conclusions

Understanding the manner in which we perceive our environment has fascinated scholars for several millennia. By the period of the Renaissance, it was already appreciated how an image is focused on the retina, and that the interpretation of it is the domain of a region in the brain. Since then research has provided a detailed understanding of the vision system; this allows us to appreciate the manner in which extreme environments affect the structure and function of the eye, and consequently vision.

The present review has focused on the direct and/or indirect effect of environmental factors on the structure and function of the eye. The manner in which these factors affect the performance of vision-dependent tasks has only been alluded to. The effect of an extreme environment on the

eye is multifactorial and, in some cases, serious. Much remains to be discovered and understood, such as the cause, prevention and treatment of Spaceflight Associated Neuro-ocular Syndrome. Without such knowledge the future of human spaceflight, habitation and our species may be constrained.

Not only are the eyes the "window of the soul" they can also reflect and predict important pathologies; as the Roman philosopher Cicero (104-43 B.C.) stated:

"Ut imago est animi voltus sic indices oculi" (the face is a picture of the mind as the eyes are its interpreter).

Additional information

Competing interests

The authors have no competing interests.

Author contributions

All authors contributed to the conception and design of the work, and to drafting the work and revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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In 2019 the UK Physiological Society celebrated achievements in the field of Extreme Environmental Physiology. The present review contributes, in part, to this important initiative.

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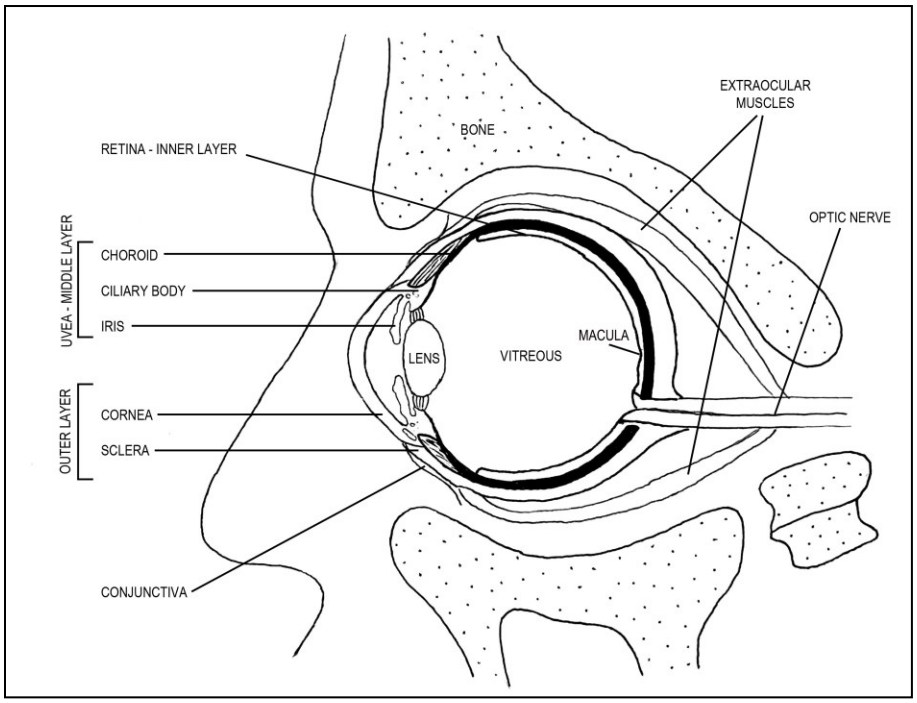

Figure 1: Basic anatomy and physiology of the eye.
The eyeball lies in the bony orbit and is surrounded with extraocular muscles, vessels and orbital fat tissue. The eyeball consists of three layers: outer fibrous tunic (white and opaque sclera which continue into transparent cornea in the anterior part), middle vascular tunic - uvea (choroidea which continue into ciliary body and into iris), and inner nervous tunic - retina. Structures of the layers enclose the refractory media: cornea, lens and vitreus humor, which refract and direct the light to specific regions of the retina, the light-sensitive layer of the eye, the macula.

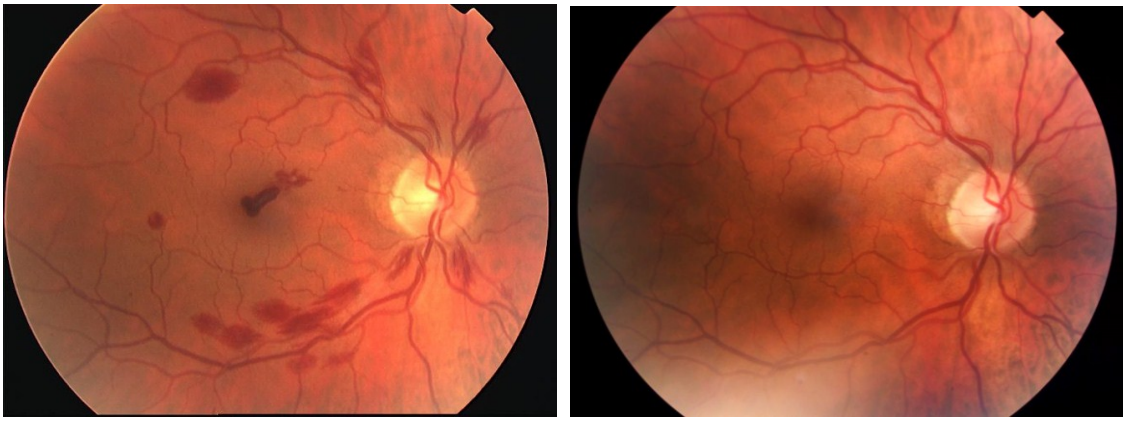

Figure 2: Fundus photograph of subject who achieved 5200 m summit.

High altitude retinopathy – HAR (left panel), and after 3 months follow-up (right panel). Numerous haemorrhages appeared in the inner retina. The haemorrhage in the central part of the retina (fovea) impaired the vision of the climber. HAR changes completely resolved.

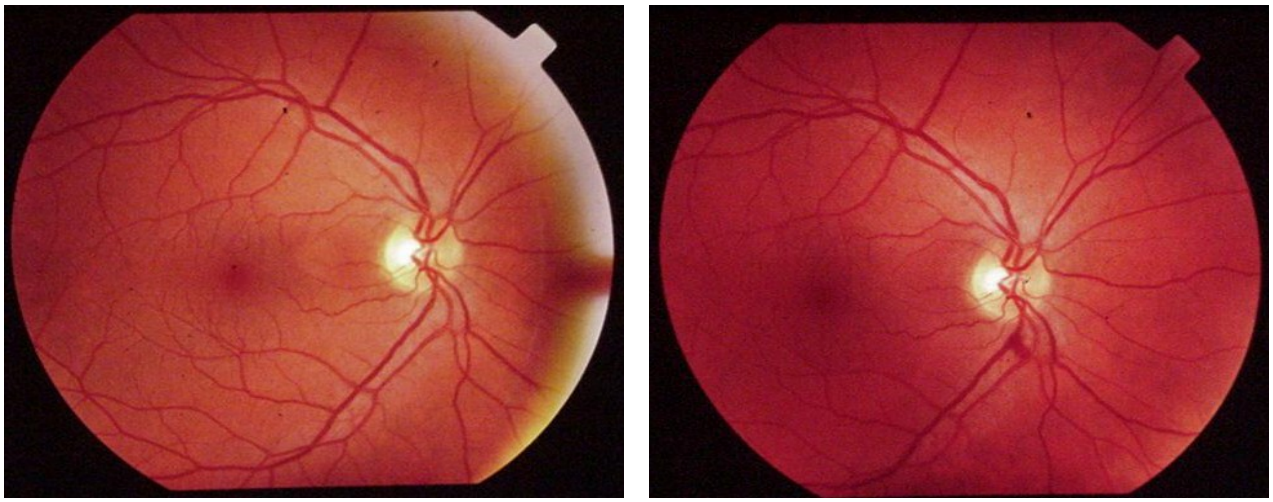

Figure 3: Fundus photographs of a member of the Ski Everest 2000 expedition before (left panel) and after (right panel) skiing from the summit of Mt. Everest to basecamp. After the expedition, a haemorrhage was visible in his retina below the optic disc. The retinopathy was not due to altitude, but due to the physical exertion.

Table 1: Environmental stressors in different extreme environments that influence vision

STRESSOR	ENVIRONMENT			
	High altitude	**Underwater**	**Aircraft**	**Space**
Wind, cold	Dry eye syndrome			
Low humidity	Dry eye syndrome		Dry eye syndrome	Dry eye syndrome
UV irradiation	Photokeratitis			
Cosmic radiation				SANS*
Hypoxia	High altitude retinopathy Refractive changes			Future habitats*
Hypercapnia				Affects retinal vessels, no known functional effects on vision
Rapid change in pressure (decompression)		Tear film bubbles Ocular barotrauma Eye manifestation of decompression illness		
Alteration in gravity			Gray-out, Black-out, Red-out	SANS
Exertion	Valsalva retinopathy		anti-G manoeuvre retinopathy	Contributes to SANS*
Long term confinement (submarines, space		Myopia		?

vehicles)				

* hypothesised effect and/or contribution

Table 2: The most often reported eye conditions in extreme environments

Eye condition	Ocular symptoms/ Signs	Prevention/ Therapy	Extreme environment
Dry eye	Sensation of the foreign body, light sensitivity, blurred vision	Blinking, topical tear substitutes, lubricating ointment, properly fitted goggles	High altitude, Desert, air conditioned Artificial environments
UV keratitis (photokeratitis, "snow blindness")	Tearing, photophobia, Blinking, delayed ocular pain	UV-blocking sunglasses; topical tear substitutes, lubricating ointment,	Snow High altitude Shallow water
Refractive changes	Blurred vision	Face mask	underwater
Ischaemic trauma to the brain (due to decompression sickness)	Nystagmus, Visual field defect, vision loss	Adherence to decompression tables / adequate aircraft pressurisation; Recompression, hyperbaric oxygen	Underwater High altitude Aircrafts
Arterial gas embolism of central retinal artery	Sudden severe loss of vision		Underwater High altitude
Ocular barotrauma	Eyelid oedema,	Adequate mask pressure	Underwater

	haemorrhage in the skin around the eyes, subconjunctival haemorrhage	equalization	
Corneal oedema	profound vision deterioration, pain		Hypoxia at altitude
High altitude retinopathy	Severe visual impairment; dilated retinal vessels, optic disc swelling, haemorrhaging in the retina and vitreous cavity	Descent with care and assistance	Altitude
Retinal hypoxia	Loss of color vision, vision becomes dim, loss of peripheral vision, total loss of vision	Straining maneuver, positive pressure breathing; normalization of the g-force	Acceleration on the Aircraft (positive g-force)
Retinal haemorrhages	Reduced vision		Natural free-fall (negative g-force)
SANS			Microgravity (ISS)