

Chapter 2

Basic sciences relevant to glaucoma

In order to understand the role of ocular blood flow (OBF) in glaucoma better, it is worth going over some of the basics.

One of the main molecules to play a role in the destructive processes of the body is, paradoxically, the oxygen molecule. This molecule can be induced to form deleterious types of oxygen molecule or reactive oxygen species (ROS) when provided with an additional electron or energy. In the context of ophthalmology, light also has a paradoxal role; it is on one hand a prerequisite for our sight, and on the other hand it is a risk factor for molecular damage. Before we probe further into the field of glaucoma, it is worth briefly outlining:

- the basic chemistry of the oxygen molecule
- the physical properties of light, and
- the concept of cellular stress.

What is a redox reaction?

Figure 2.1a shows a reduction/oxidation (or redox) reaction. The term oxidation refers to the loss of electrons and reduction refers to the gain of electrons. Pro-oxidants are molecules which can oxidize other molecules (ie, they are molecules with an oxidizing potential that is stronger than the oxidizing potential of the molecule they react with). Pro-oxidants can be in the form of free radicals as in the case of superoxide, $O_2^{\cdot-}$ (Figure 2.1b) or non-radical species (eg, hydrogen peroxide H_2O_2 , or ozone O_3). Free radicals are molecules that contain one or more unpaired electrons. Although the chemical reactivity of free radicals varies, the need of the molecule to pair-up the unpaired electron can make free radicals highly reactive.

The eye is a unique organ and although biologically part of the brain it is directly exposed to the environment. In addition, exposure to light is necessary for it to function. The concentration of oxygen is high, both in

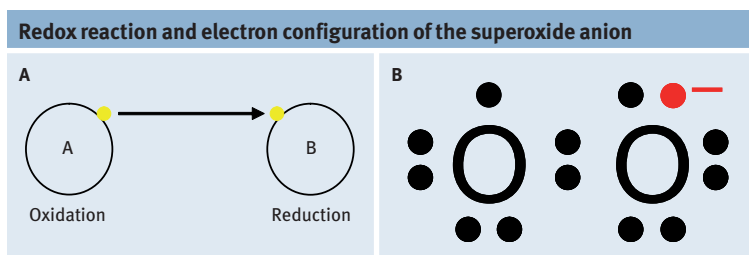


Figure 2.1 Redox reaction and electron configuration of the superoxide anion.

A, redox reaction. Oxidation describes the loss of electrons by a molecule, atom or ion. Reduction describes the gain of electrons by a molecule, atom or ion. **B**, electron configuration of the superoxide anion. The unpaired electron is shown in the upper left and the additional electron conferring a negative charge is shown in red.

the anterior part of the eye which is exposed to the environment, and in the choroids with its dense network of blood vessels. Energy metabolism involving oxygen can generate a potentially damaging, ROS (ie, pro-oxidants) as illustrated in Figure 2.2. Under optimal conditions the formation of ROS is balanced by the rate of oxidant elimination by available the antioxidants. An antioxidant is by definition any substance, that when present at a lower concentration than an oxidizable substrate, significantly delays or prevents oxidation of that substrate. In very simple words, an antioxidant can neutralize pro-oxidants. However, even in healthy subjects ROS may cause some macromolecular damage. An imbalance between pro-oxidants and antioxidants, in favour of the former, results in oxidative stress which damages molecules and leads to up-regulation of the antioxidative system. This will be discussed in more detail in Chapter 3.

What is the role of light?

Light comprises a very small section of the broad electromagnetic field spectrum that can be perceived by our eyes and consequently interpreted by our brain as light. For example, we can see a star because it emits light which eventually finds its way into our eyes. A book placed on a table is visible because it absorbs, scatters, and also reflects the light differently than the table. While the effect of light can easily be recognized it remains difficult to understand the nature of light. From a physical point of view, light can be described either as a small corpuscle (photon) or as an electromagnetic wave (Figure 2.3). Light is the basis for vision and also provides energy, through photosynthesis, to plants. Unfortunately, light can also have a detrimental effect. The following sections discuss how energy from light can transform

The eye exposed to oxidative stress

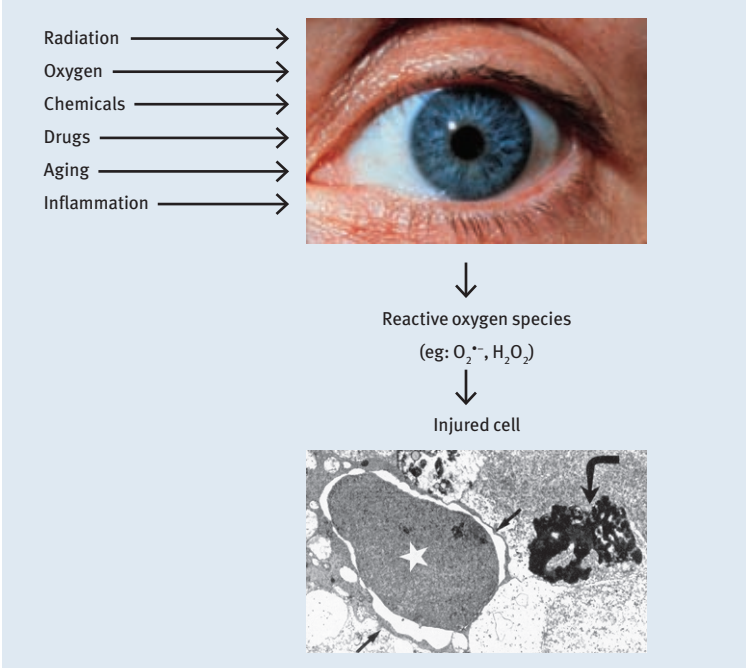


Figure 2.2 The eye exposed to oxidative stress. The eye is an organ that is predisposed to great levels of oxidative stress. The eye is constantly exposed to factors which induce the formation of reactive oxygen species that can ultimately damage cells.

relatively inert molecules or atoms into damaging ROS. The specific role of free radicals in the pathogenesis of glaucomatous optic neuropathy (GON) will also be discussed.

The oxygen molecule

The oxygen molecule in the earth's atmosphere

The oxygen in the earth's atmosphere increased as it was released from water by cyanobacteria (blue-green algae) more than a billion years ago. Cyanobacteria are photosynthetic and aquatic. These bacteria used light as an energy source for their metabolism (ie, photosynthesis) and in order to gain protons (eg, for the synthesis of carbon-hydrates) they split water molecules, and thereby released tonnes of oxygen into the atmosphere (Figure 2.4).

When living organisms first appeared on earth, they did so under an atmosphere containing very little oxygen (ie, they were anaerobes). Anaerobic

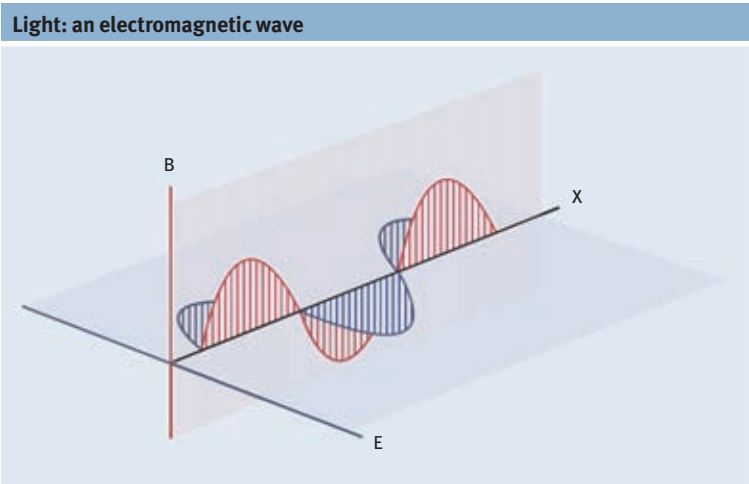


Figure 2.3 Light: an electromagnetic wave. Electromagnetic waves are formed when an electric field (shown as blue) couples with a magnetic field (shown as red).

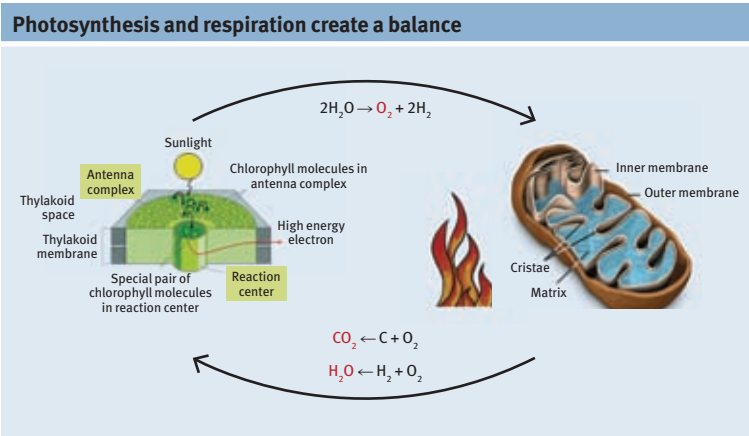


Figure 2.4 Photosynthesis and respiration create a balance. Photosynthesis uses energy from sunlight to liberate oxygen (O_2) whereas respiration gains energy by using O_2 .

organisms still exist today but their growth is limited and they can be killed by the current atmospheric level of 21% oxygen. The damaging effect of oxygen on strict anaerobes seems to be due to the oxidation of essential cellular compounds. As the oxygen content of the atmosphere increased, many primitive organisms must have died out. Eukaryotic organisms began

the evolutionary process of using both oxygen, and adapting to higher oxygen concentrations in the atmosphere. Oxygen is used to gain energy by oxidizing other molecules such as protons, however this resulted in the production of some unwanted ROS. Organisms that tolerated the presence of oxygen were naturally selected over others; these organisms developed antioxidant defenses and developed through the evolution of the electron transport chain (ETC). For energy production they developed the electron transport chain where oxygen was used as the terminal electron acceptor, enabling the oxidation of 'food' more efficiently. The development of the ETC first developed in bacteria and then evolved further by endosymbiosis of bacteria (mitochondria are descendants of bacteria) in eukaryotic host cells (Figure 2.5). In a similar way, the chloroplasts of plants originated by endosymbiosis of bacteria.

When is the oxygen molecule beneficial and when is it harmful?

The oxygen molecule is considered to be the elixir of life and this benign image is well deserved, as long as the molecule remains in its electronic ground state. By adding energy to this molecule, the electron configuration is changed to an electronically excited state. As this molecule is now more reactive it belongs to the ROS and becomes damaging, particularly if it is in excess of the cellular antioxidant balance. The oxygen molecule in its ground state however is quite inert although it is a (di-)radical.

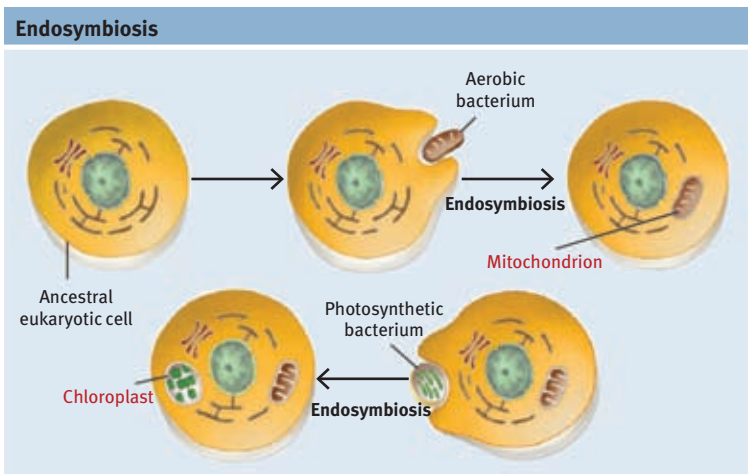


Figure 2.5 Endosymbiosis. The mitochondria and chloroplasts of eukaryotes evolved from ancient endosymbiosis of aerobic bacteria by the ancestral eukaryotic cell.

As mentioned earlier, a free radical is an atom or a molecule with an unpaired electron in its outer shell. By gaining or losing an electron, free radicals maintain a much more stable electronic configuration which explains their reactivity. The question therefore arises as to why 'normal' atmospheric oxygen is only minimally reactive? In its ground state the oxygen molecule has two unpaired electrons, each of which are located in a different pi antibonding orbital (Figure 2.6). These two electrons rotate about their own axis in the same direction (ie, they have the same or parallel spin). When two free radicals fuse to form a new molecule, the electrons of the two molecules that will pair together have a different (anti-parallel) spin. The oxygen molecule would need another molecule with two electrons with the same spin, which are both anti-parallel to the spin of the electrons of the oxygen molecule. This, however, is very rare and it is this spin restriction which makes molecular oxygen in its ground state normally non-reactive. Oxygen molecules become reactive if they gain either energy (eg, in the case of a fire) or if they accept one individual electron (eg, as in the production of superoxide).

How can oxygen be activated in biological tissues?

Oxygen can be activated by two different mechanisms: through the absorption of sufficient energy to reverse the spin on one of the unpaired electrons, or through monovalent reduction (Figure 2.7).

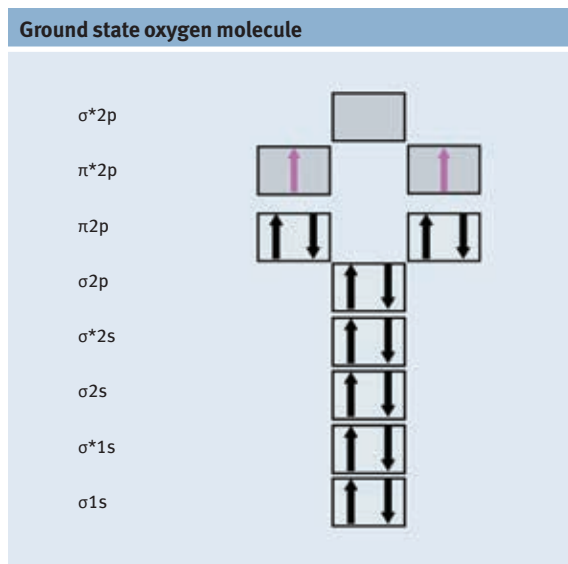


Figure 2.6 Ground state oxygen molecule. In ground-state, the last two unpaired electrons have the same quantum spin number (ie, they have parallel spins).

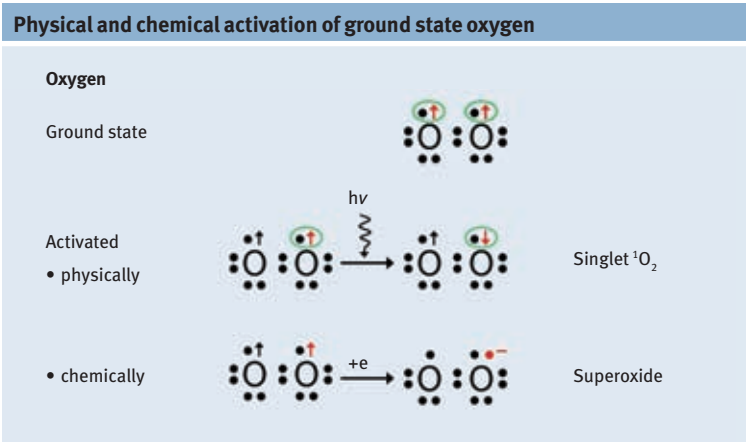


Figure 2.7 Physical and chemical activation of ground state oxygen. The oxygen molecule can be activated physically (eg, direct excitation by light) to form the singlet oxygen, or it can be activated chemically by a reduction reaction (eg, one electron reduction of dioxygen) to form the superoxide anion.

If ground state oxygen absorbs sufficient energy to reverse the spin of one of its unpaired electrons, the two unpaired electrons now have opposite spins. This activated form of oxygen, known as singlet oxygen ($^1\text{O}_2$) is much more reactive than ground state oxygen and reacts, for example, with molecules which have double bonds. The damaging effect of ROS can also be used in a beneficial manner. For example, in photodynamic therapy the photosensitizer, activated by light, can deliver its energy to a nearby oxygen molecule in ground state, converting it to the reactive singlet oxygen. This in turn destroys unwanted neovascularizations (Figure 2.8).

The second mechanism of activation is by the stepwise monovalent reduction of oxygen which gives rise to the superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2), and finally to water (H_2O) as shown in Figure 2.9.

Hydrogen peroxide is a molecule with a high oxidizing capacity. Many transformations are also facilitated by enzymes or by metal atoms.

The concept of cellular stress

What happens when a cell is subjected to stress?

All diseases, including glaucoma, are based on the functional or structural damage of cells. Damaging factors include hypoxia, toxins, ionizing radiation, viruses, and bacteria or immune processes. Cells respond to stress in a limited number of ways as shown in Figure 2.10. If the stress induced is high, the cell

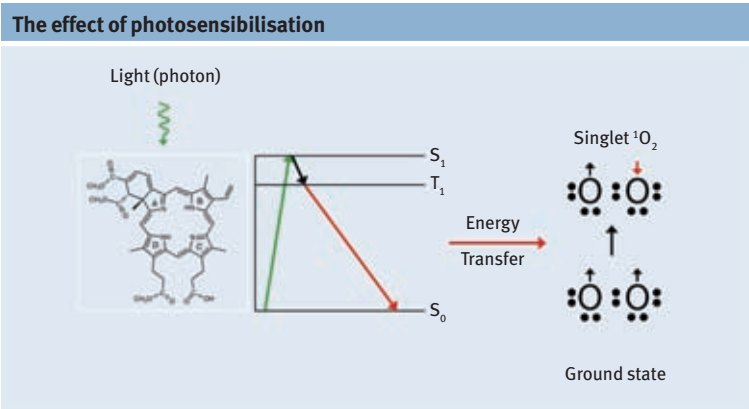


Figure 2.8 The effect of photosensibilisation. A photosensitizer (eg, verteporfin) can absorb light. Once activated, the photosensitizer can transfer a part of this energy to an oxygen molecule to produce singlet oxygen.

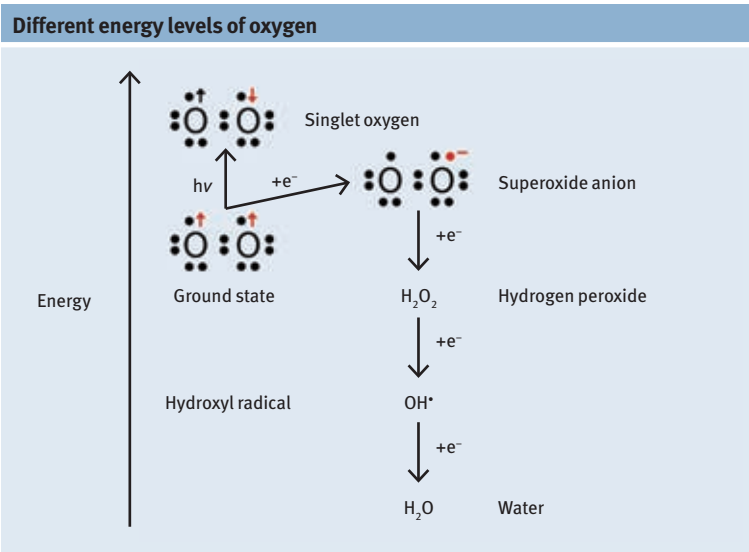


Figure 2.9 Different energy levels of oxygen. Activation of oxygen occurs either through absorption of light or through reduction.

dies either by necrosis or apoptosis. If the stress is moderate, the cell survives but it temporarily changes its gene expression, and may lead, for example, to an increased production of heat shock proteins. These proteins act as molecu-

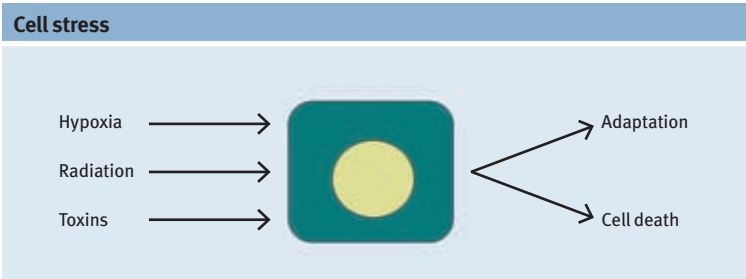


Figure 2.10 Cell stress. In response to stress a cell can either adapt or die.

lar chaperones protecting the three-dimensional structure of other proteins. Repeated or chronic cellular stress leads to a chronic ‘response to injury’ and according to the level of stress, can lead to preconditioning, metaplasia, dysplasia or even apoptosis. Depending on the tissue the extracellular matrix is also involved leading to tissue remodeling. These tissue changes are often accompanied by cellular loss. In vitro, it has been shown that mechanical, biochemical or ischemic stress induces a similar cellular response. Such changes can also be observed in human GON, especially in the glial cells.

Oxidative stress

What is oxidative stress?

The eye is exposed to light, a high concentration of oxygen, environmental chemicals and physical abrasion. As mentioned previously, the metabolism of oxygen by cells generates potentially harmful ROS. Under optimal conditions the rate and magnitude of oxidant formation is balanced by the rate of oxidant elimination through the action of antioxidants. Nature has therefore provided us with mechanisms to help us cope with pro-oxidants. If ROS production exceeds this capacity, however, oxidative stress will occur (Figure 2.11).

As long as nature is capable of repairing damaged molecules (eg, DNA) or eliminating damaged molecules (eg, proteins via proteasomes) no major structural damage will occur. If, however, oxidative stress exceeds the capacity of repair mechanisms, structural damage will accumulate and result in damage that is ultimately clinically relevant and which we term a disease, as illustrated in Figure 2.12.

There are several ways to gain information about oxidative stress (eg, quantifying the amount of antioxidants or indirectly measuring the oxidation of certain molecules such as lipids), we will focus here on the comet assay methodology, which looks at the number of breaks in DNA.

Coping with reactive oxygen species

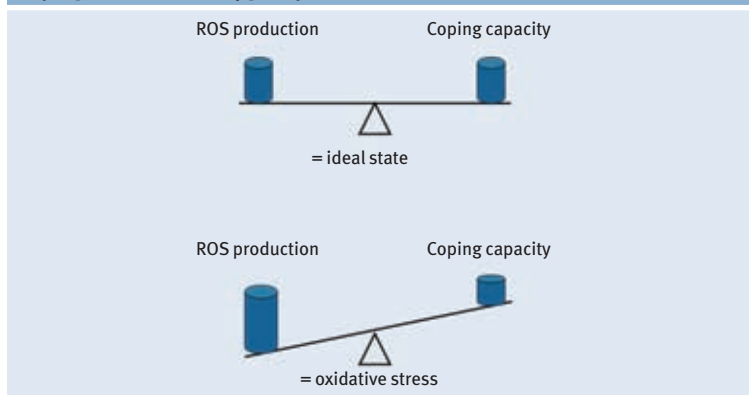


Figure 2.11 Coping with reactive oxygen species. ROS, reactive oxygen species. Nature has provided us with mechanisms to cope with ROS. If ROS production, however, exceeds this capacity, oxidative stress results.

The role of the repair system

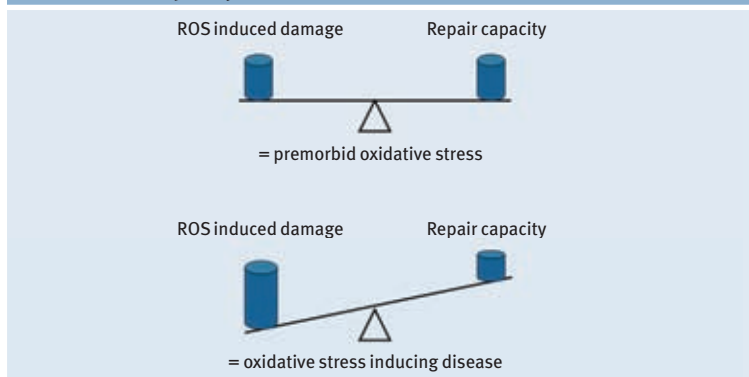


Figure 2.12 The role of the repair system. ROS, reactive oxygen species. As long as the repair capacity exceeds the induced damage no disease will develop. If oxidative-induced damage exceeds the repair capacity a disease may develop.

Comet assay

Comet assay, also known as single cell gel electrophoresis, allows measurement of DNA breaks, induced by different factors such as radiation and oxidative stress. If these factors known to cause DNA damage are weak and kept constant, the amount of DNA damage measured by comet assay is a good parameter of oxidative stress.

The principle is simple and relies on the fact that DNA molecules are negatively charged. An intact DNA molecule has such a large size that it does not migrate towards the anode in electrophoresis. However, if breaks are present in the DNA the resulting smaller fragments move in the electrical field towards the anode; the smaller the fragment, the faster the migration. As the fragments have different sizes the final result of the electrophoresis is not a distinct line but rather a continuum with the shape of a comet. This method allows the resulting 'comet' to be measured and assessed.

How is comet assay performed practically?

A sample of blood is drawn from the subject by venipuncture, and leukocytes are isolated from the sample. The cells under study are embedded in agarose on a slide and subjected to lysis, followed by electrophoresis. Finally, to visualize DNA, the slides are stained with propidium bromide and examined by fluorescence microscopy equipped with a computer-based analysis system which accurately enables the number of DNA breaks to be counted (Figure 2.13).

Assessment of ocular blood flow

While it is possible to measure OBF, it is not simple. Methods used today are based on a number of physical principles and measure different aspects of OBF in various tissues of the eye. The discussion here will be limited to some of the more commonly used methods.

When performing measurements of blood flow in the eye, we can take advantage of optical phenomena. Measurements behind the eye rely on ultrasound. Most methods primarily calculate blood flow velocity and, although the relationship is not always strictly proportional, in general lower blood flow velocity indicates a lower blood flow (Figure 2.14).

There is still debate over which vascular bed is most relevant in the case of glaucoma although it is most likely to be the optic nerve head (ONH). Given that OBF outcome measures in different parts of the eye correlate quite well with each other, the selection of the measuring field may not be that relevant. There is even a correlation between OBF and blood flow in the fingers, at least in subjects with vascular dysregulation. Although OBF in patients with glaucoma is, on average, different from healthy subjects at baseline, these differences become much more evident when OBF is challenged in a provocation test.

Measuring temperature

The temperature of any organ, particularly in the extremities, is related to a number of factors including blood flow.

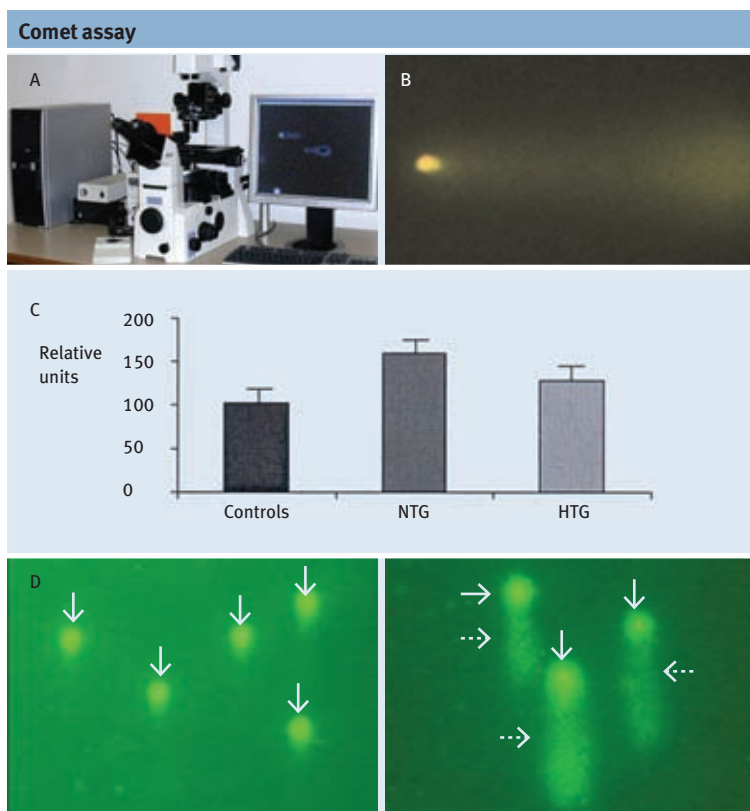


Figure 2.13 Comet assay. HTG, high tension glaucoma; NTG, normal tension glaucoma. Comet assay is a micro gel electrophoresis technique which allows quantification of DNA breaks. **A**, equipment. **B**, an example. **C**, increased DNA breaks in the lymphocytes of patients with glaucoma. **D**, photo showing the lymphocytes of a control patient (left), and a patient with glaucoma (right). The dashed arrows show the resulting 'comets' in the DNA of the patient with glaucoma which is a good indicator of oxidative stress.

Reports indicate that the eyes of patients with glaucoma, particularly patients with normal tension glaucoma (NTG), are cooler than those of patients without glaucoma (Figure 2.15). Furthermore, reports also show that an increase in OBF, induced directly pharmacologically or by decreasing IOP, increases corneal temperature.

Fluorescence angiography

Fluorescence angiography (FLA) is normally used to determine if there is an alteration in any of the ocular vessels (eg, occlusions, decrease in barrier func-

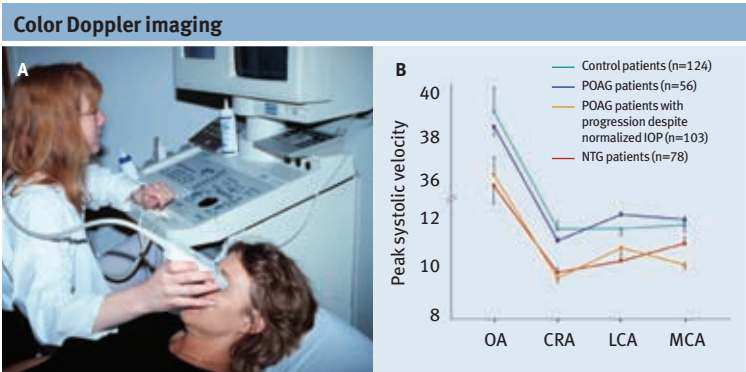


Figure 2.14 Color Doppler imaging. CRA, central retinal artery; LCA, lateral ciliary artery; MCA, medial ciliary artery; OA, ophthalmic artery. **A**, representation of its clinical use. **B**, peak systolic velocity in the different retroocular vessels. The graphs represent the mean (\pm SD) of the different groups.

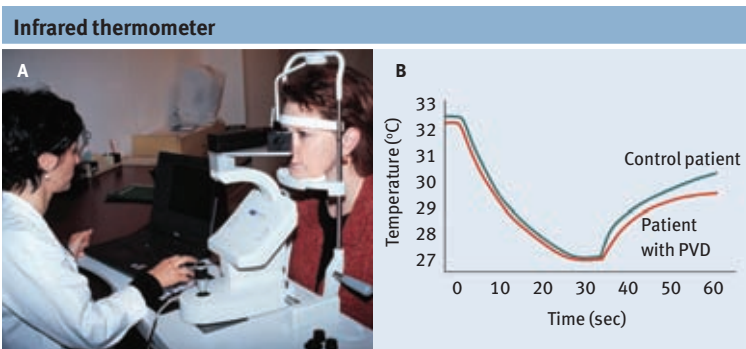


Figure 2.15 Infrared thermometer. PVD, primary vascular dysregulation. **A**, representation of its clinical use. **B**, after cooling the cornea with an air stream, patients with PVD have a prolonged re-warming time.

tion, microaneurysma). FLA is not used routinely for patients with glaucoma, nevertheless studies with FLA have demonstrated the following alterations in these patients:

- a reduction in blood flow velocity as demonstrated by delayed filling (ie, prolonged arm retina time) and as prolonged arteriovenous passage time;
- filling defects in, and around, the ONH in the juxtapapillary area (Figure 2.16); and
- increased leakage impairment of the blood–brain and blood–retinal barrier (Figure 2.17)

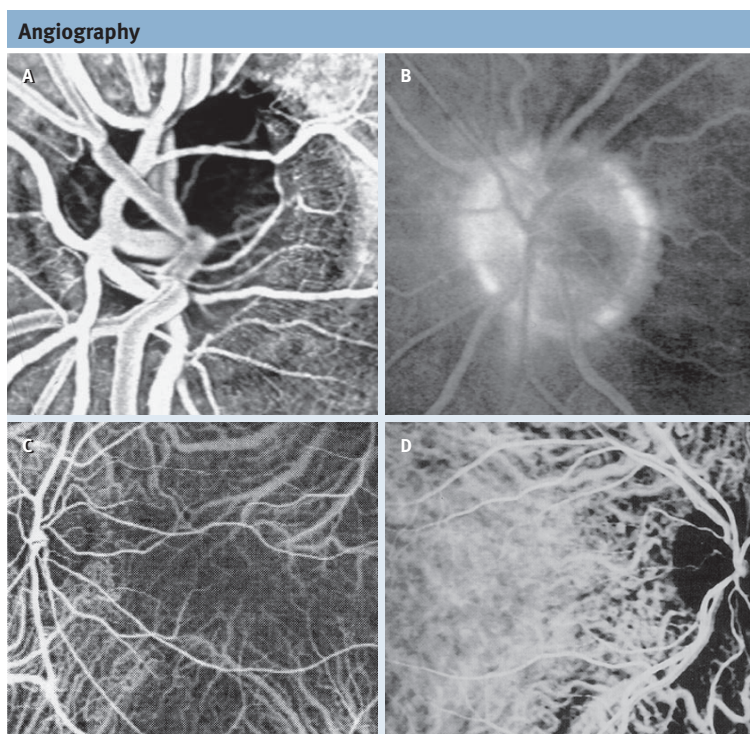


Figure 2.16 Angiography. **A**, fluorescence angiography of a glaucomatous papilla, parts of the optic nerve head are not perfused. **B**, mild diffuse staining. **C, D**, indocyanine angiography in a glaucomatous eye, delayed filling of some of the choriocapillaries.

Retinal vessel analyzer

The retinal vessel analyzer is an instrument that quantifies the size of retinal arteries and veins along a selected segment over a period of time (Figure 2.18). The vessel diameter provides only indirect information about OBF. Nevertheless, the size of arteries and veins, and their spatial and temporal variation, provides very useful information which can be used to study in depth whether a provocation or treatment dilates or constricts a vessel.

The Doppler effect

The Doppler effect was first described by the Austrian scientist Christian Doppler in 1842. Doppler observed the fact that the light emitted from a star moving away from us would have a slightly longer wavelength (ie, a shift towards the red end of the electromagnetic spectrum) than the light of one moving towards us (ie,

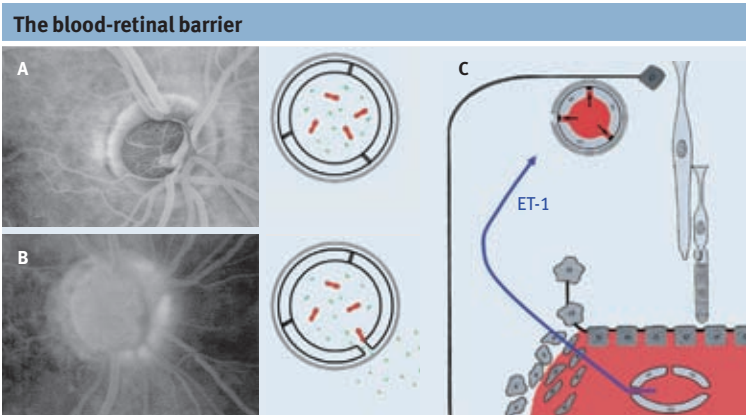


Figure 2.17 The blood-retinal barrier. ET-1, endothelin-1. **A**, in contrast to the choriocapillaries, retinal vessels have a dense blood retinal barrier. **B**, in glaucoma the barrier is partially opened as a result of diffusion of ET-1 into this area. **C**, line drawing of B.

a shift towards the blue end of the electromagnetic spectrum). The ‘Doppler-effect’, describes a frequency shift of waves of any nature (eg, light, acoustic, water) emitted from an object which is moving away or towards an observer (Figure 2.19). Today, with lasers providing optical light waves of extreme purity, it is possible to detect Doppler shifts with very high resolution. A continuous laser light is projected into a tissue and the backscattered light is analyzed; this light contains two components:

- shifted light – scattered by moving particles such as blood cells
- unshifted light – scattered by relatively stationary structures (eg, vessel walls).

Most of the light is backscattered without a shift in frequency. Moving particles, however, cause a Doppler shift on scattered light. The relative number of shifted photons depends on the number of moving particles (in our case blood cells) whereas the size of the shift depends on the velocity of these particles. The laser Doppler principle can therefore be used to measure blood flow velocity and to some extent OBF itself.

Laser Doppler velocimetry

Laser Doppler velocimetry (LDV) is a technique that measures blood flow velocity by directing a laser beam at a selected blood vessel. The blood flowing through the vessel causes a Doppler shift, or change in wavelength, allowing the speed of the blood to be measured. If in addition, the diameter of the vessels is measured, blood flow can be calculated.

The retinal vessel analyzer

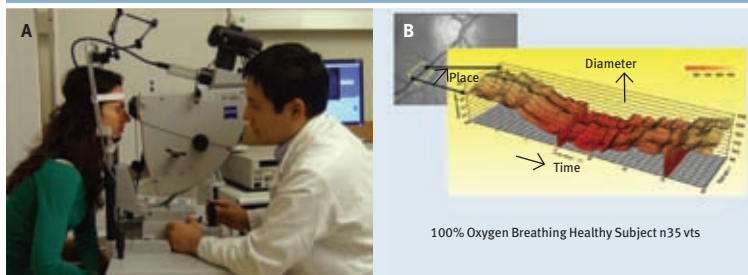


Figure 2.18 The retinal vessel analyzer. A, representation of its clinical use. B, the retinal vessel diameter of a vascular section using the retinal vessel analyzer. Constriction resulted after the patient breathed in 100% oxygen.

Principle of the Doppler effect

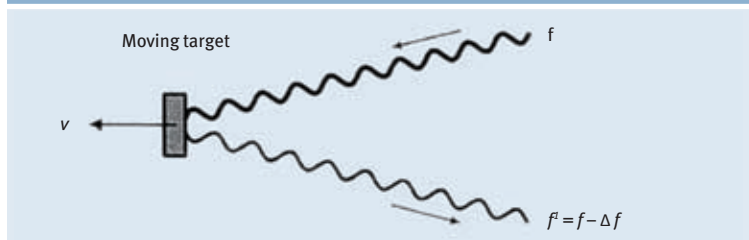


Figure 2.19 Principle of the Doppler effect. A laser beam reflected by a moving object returns with a frequency change, Δf , known as Doppler shift. The velocity, v , can be determined from Δf .

Laser Doppler flowmeter

Laser Doppler flowmetry (LDF) is based on the fact that the size of the shift depends on the velocity of the moving particles and the relative amount of light that is shifted depends on the number of moving particles (Figure 2.20). Based on these two variables, a third variable, the so-called “flux” can be calculated. Unlike velocimetry, flowmetry measures the blood flow in capillary beds. The laser is directed to the areas between larger vessels and can be applied either to the ONH or to the retina. Blood flow in the choroid, however, can be measured only in the subfoveal area and by using a longer wavelength. LDF is best suited for intra-individual comparisons.

Color Doppler imaging

As light cannot reach the tissues behind the eye, ultrasound is used to measure blood flow velocity in the retroocular vessels (Figure 2.21).

Laser Doppler flowmetry

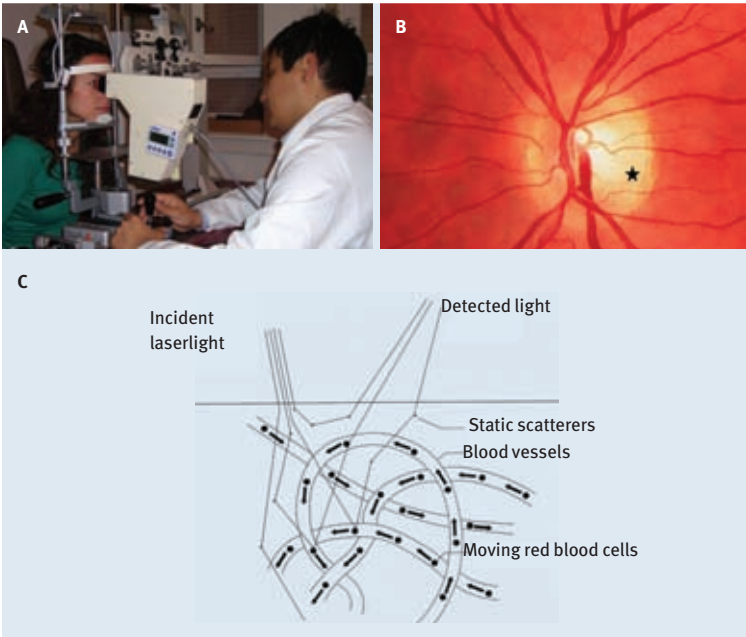


Figure 2.20 Laser Doppler flowmetry. A, representation of its clinical use. B, laser Doppler flowmetry measures flow at a selected point (*). C, a portion of the scattered light eventually leaves the tissue in the direction of the detector.

Color Doppler imaging

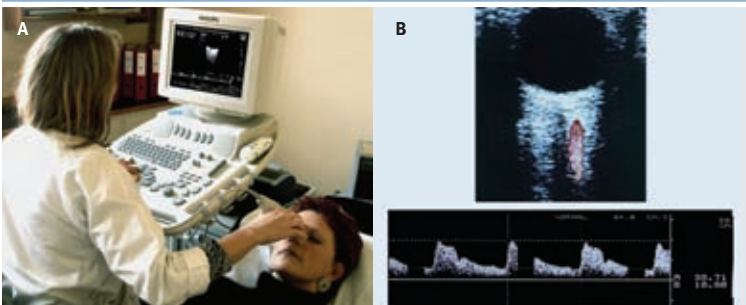


Figure 2.21 Color Doppler imaging. A, representation of its clinical use. B, color coding of flow direction superimposed on a B-scan (top). Blood flow velocity in a selected vessel (bottom).

A color Doppler is a device that combines imaging with a B-scan, localization of blood flow based on a Doppler principle, and quantification of blood flow velocity with pulsed Doppler technique. This is the technique used most often today for patients with glaucoma.

Ocular pulse amplitude

Ocular pulse amplitude (OPA) can be measured using a variety of methods (Figure 2.22). These techniques, however, will not be discussed any further here as, at present, there is limited information concerning the relationship between OPA and OBF.

Nailfold capillaromicroscopy

Capillaromicroscopy is an old technique used by angiologists to quantify the blood flow velocity in the capillaries of the extremities (Figure 2.23).

The fact that the capillaries in the nailfold are arranged in a unilayer and are parallel to the surface and therefore perpendicular to the observer makes it very easy to measure blood flow in this area. How then is blood flow in the nailfold capillaries related to OBF? In the past, before OBF measurements were possible, the relationship between nailfold capillary blood flow and visual field had already been observed in certain patients. It was assumed, therefore, that there could be a relationship between blood flow in the fingers and in the eye. Today, we know that such a relationship does indeed exist in patients with primary vascular dysregulation (PVD). Nailfold capillaromicroscopy can be used, therefore, to some extent as a substitute for OBF. However, it is most often used to test for dysregulation.

Visual field changes as a parameter for ocular blood flow

It may seem strange for perimetry to be listed among the methods used to quantify OBF. Perimetry is used to measure differential light sensitivity (DLS)

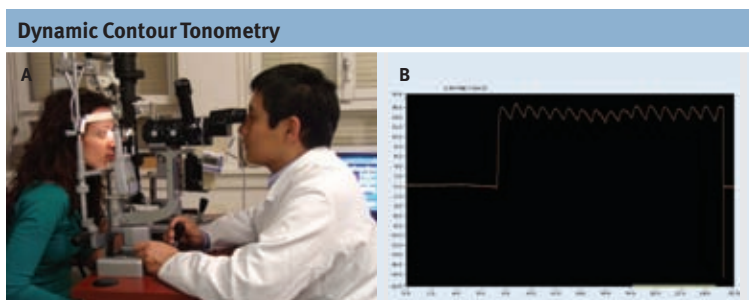


Figure 2.22 Dynamic Contour Tonometry. A, representation of its clinical use. B, output depicting ocular pulse amplitude.

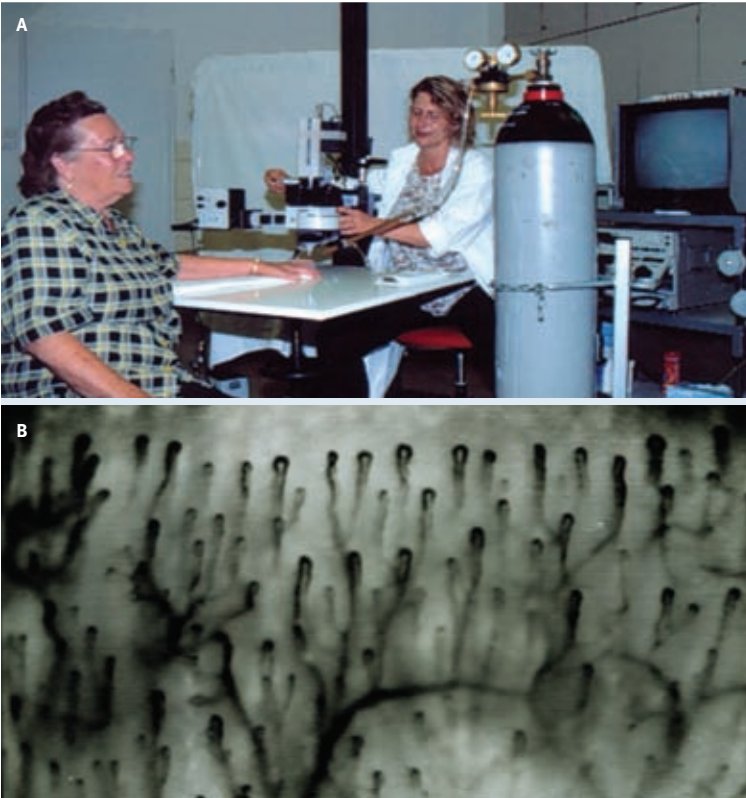
Nailfold capillaromicroscopy

Figure 2.23 Nailfold capillaromicroscopy. **A**, representation of its clinical use. A microscope coupled to a television monitor, allows the observed blood flow to be videotaped and to be analyzed off-line. Cold compression is induced by decompression of gas. **B**, a closure of one or more of the visible capillaries can be detected on the video screen.

in the visual field (Figure 2.24). The outcome fluctuates in normal eyes and this fluctuation is amplified in patients with glaucoma. The fluctuation has both a short- and long-term component. The short term component depends on factors such as damage of the visual field or cooperation of the patient, whilst the long-term component seems to be, among other factors, influenced by ocular circulation. DLS is also strongly related to blood-oxygen tension and the DLS threshold fluctuates in parallel with IOP. In patients with vascular dysregulation, the improvement observed in the visual field while undergoing vasoactive

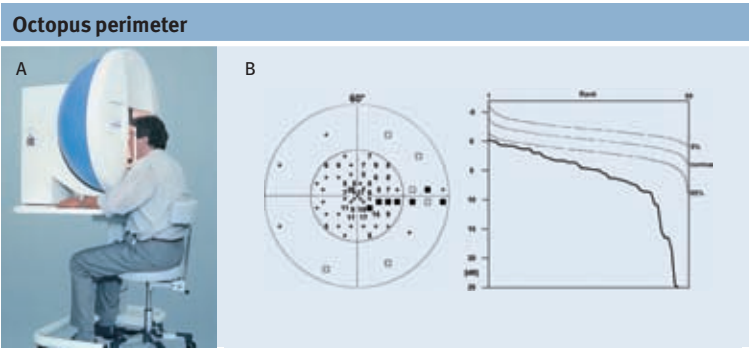


Figure 2.24 Octopus perimeter. **A**, representation of its clinical use. **B**, output of an Octopus G1 program (left) and representation of the same visual field by the Bebie curve (right).

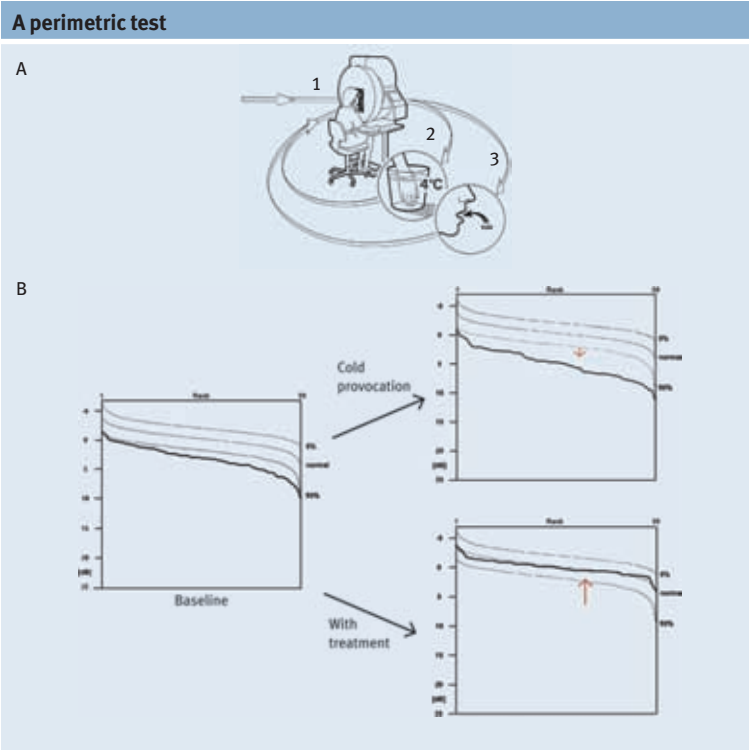


Figure 2.25 A perimetric test. The visual field is represented by a Bebie curve of a patient with primary vascular dysregulation. **A**, schematic representation of a perimetric test (1) after cold provocation (2) and after treatment (3). **B**, baseline values (left), deterioration after cold provocation (top right), improvement after treatment with calcium channel blockers (bottom right).

treatment (eg, with calcium channel blockers) correlates to the changes in blood flow observed in the periphery. Likewise, deterioration of the visual field after cold provocation also correlates with blood flow deterioration. A relatively quick (reversible) change in the visual field can therefore be an indirect sign of a change in ocular perfusion (Figure 2.25).

Provocation tests

When measuring blood flow it is important to be aware that blood flow in a given tissue is not constant. OBF depends upon a number of factors such as exposure to light, environmental temperature, physical activity or emotional status. In certain patients blood flow may be within normal limits when measured under baseline conditions. If blood flow is measured under challenging conditions the regulation may not be to the same extent as in healthy controls. Provocation tests, therefore, provide other and more relevant information than baseline measurements. The various provocation tests used to challenge blood flow include:

- artificially increasing IOP (induced by a suction cup)
- stimulating the autonomic nerves with a hand grip (Figure 2.26)
- coldness (eg, by blowing cold air) which is a standard procedure in nailfold capillaromicroscopy (Figure 2.27).

In patients with vascular dysregulation blood flow in the fingers correlates very well with OBF and consequently can be used as a proxy measurement.

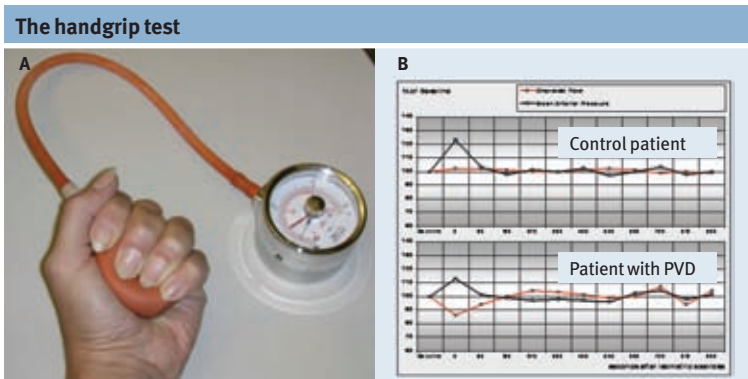


Figure 2.26 The handgrip test. A, an increased sympathetic tonus is induced by hand grip. B, choroidal blood flow (measured with laser Doppler flowmetry) remains stable (red line) in non-PVD controls despite an increase in blood pressure (blue line) (top right). There is a temporary reduction in ocular blood flow in subjects with PVD (bottom right).

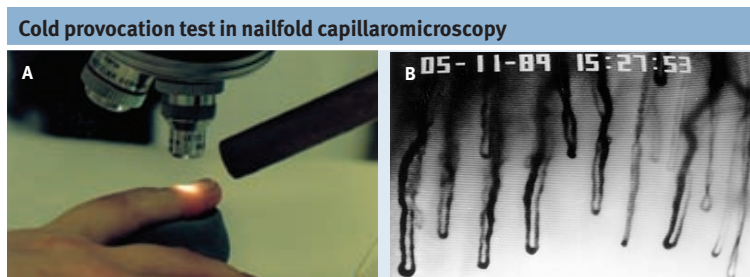


Figure 2.27 Cold provocation test in nailfold capillaromicroscopy. **A**, the nailfold is made transparent with a drop of oil. **B**, picture of the nailfold capillaries, taken from the monitor of the video nailfold capillaromicroscopy.

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