PERSPECTIVE

Ocular blood flow measurement

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Many techniques have been devised to measure the haemodynamics of the human and animal eye. In this perspective these are outlined and their use in ophthalmic investigation summarised. Some have exploited the ability of an observer to directly visualise the retinal vasculature by optical means, others have been designed to study the haemodynamics of the invisible parts of the eye such as the choroid, optic nerve head, and ciliary body. Although useful in ophthalmic investigation, none have satisfied all of the requirements of the researchers in this field and most have not achieved regular use in clinical practice.

In any examination of blood flow a multitude of variables must be studied (Table 1). The interrelation of these variables must be determined while considering physical or physiological principles (Table 2) which are often not strictly applicable to the vasculature – for example, the Hagen Poiseuille law was described for a rigid tube and not for elastic walled tubes such as blood vessels. In the human, study of the circulation is further hindered by the requirement for a non-invasive and safe method for obtaining measurements.

Study of the haemodynamics must be performed if we are to understand the mechanisms leading to the large variety of vascular diseases which affect the eye. The blood flow to the eye is of particular interest because:

- (1) Many localised and systemic disorders affect the vasculature of the eye.
- (2) The eye has unusual haemodynamic properties because the tissues are subjected to a high intraocular pressure.
- (3) Ocular blood flow is autoregulated – for example, during changes in retinal illumination, blood pressure, or posture.
- (4) Pharmacological agents which are routinely used in systemic and ocular diseases may affect the blood supply of the eye.

Techniques for the measurement of ocular blood flow

Many ingenious and varied techniques exist for the measurement of ocular blood flow. Some are restricted to experimental studies on animal models because of their destructive or invasive nature. For example, unlabelled or radioactively labelled microspheres in cats,^{1,2} dogs,³ and monkeys^{4,6} may be injected into the left ventricle of the heart and after the animal

is sacrificed, histological or radiographic measurement of the density of the microspheres is performed to allow an estimation of blood flow. Dye enclosed within heat labile liposomes has also been used to examine flow in localised areas of the retina⁷⁻⁹ and involves an intravenous injection and release of the dye from the liposomes using laser light of the appropriate wavelength. The velocity of the dye as it passes through the vessel is recorded allowing a calculation of flow if the diameter of the vessel is measured. Radioactive tracers and radiography have also been employed – for example, ¹⁴C iodoantipyrine has been used to estimate optic nerve blood flow in cats.¹ By cutting a hole in the sclera blood velocity measurements have been taken from the retinal circulation.¹⁰ The Fick principle using nitrous oxide concentrations in uveal blood samples has also been employed.¹¹

These methods are invasive and not applicable to the investigation of the human for obvious reasons. The minimally invasive procedure of fluorescein angiography remains

Table 2 Physical and physiological principles in blood flow

Flow (Q)=velocity×cross sectional area

Ohm's law

$$Q = \frac{\text{pressure difference}}{\text{resistance}}$$

Reynold's number (R) (turbulence)

$$R = \frac{p2rV}{n}$$

Hagen Poiseuille law

$$Q = \frac{(P_a - P_b)}{L 8 n}$$

$$\text{resistance} = \frac{L 8 n}{\pi r^4}$$

Laplace's law

$$\text{transmural pressure} = \frac{\text{wall tension}}{r}$$

where

p=density of the fluid
r=radius of the tube
V=velocity of the fluid
n=viscosity of the fluid
P_a-P_b=pressure difference
L=length of the tube

Bernoulli's principle:

a constriction of a vessel causes a conversion of pressure into kinetic energy thereby increasing the velocity and decreasing the pressure of the fluid in the vessel.

Doppler equation

$$V = \frac{Df c}{2 F_o \cos A}$$

where

V=velocity
Df=Doppler frequency shift
c=propagation frequency
F_o=transmit frequency
A=angle of incidence of Doppler beam to direction of flow

Table 1 Some of the measurements which might be required to allow an assessment of the haemodynamics of the ocular circulation

Haemodynamic measurements
Vessel length
Vessel cross sectional area
Blood pressure
Blood flow
Pulsatile flow
Intraocular pressure
Vessel wall tension
Resistance to flow
Blood viscosity
Turbulence
Critical closing pressure

Figure 1 The dye bolus intensity curves from a fluorescein angiogram of an adjacent retinal arteriole (E) and venule (F) are shown from a patient with central retinal vein occlusion. The delay between the two curves provides a measure of the rapidity of the flow through the retinal circulation.

the mainstay of clinical vascular investigation and has resulted in a number of techniques for the estimation of retinal blood flow. In particular, the time required for the dye to pass through the circulation has been estimated. Dye dilution curves produced from the intensity of the fluorescence in the retinal vessels have been calculated,¹² more recently employing videoangiography and computerised image analysis.^{13,14} Two curves of the intensity of fluorescence are plotted against time, for example from a retinal arteriole and an adjacent venule (Fig 1) and the time delay between these two curves measured at various intensity levels of the dye – for example, at 0%, 25%, 50%, 75%, and 100% of the peak fluorescence.¹⁵ The time delay between the passage of dye is presumably inversely proportional to the blood flow rate through the retinal vessels therefore providing a measure of the retinal haemodynamics.

The temporal resolution of the scanning laser ophthalmoscope has been exploited to allow measurement of macular blood velocities from fluorescein angiography.^{16–18} This has been performed by injecting a bolus of dye and measuring the velocity of fluorescent white blood cells or gaps in columns of red blood cells as they pass through the perifoveal capillaries. These may be travelling at different speeds dependent on the orientation of the vessel; therefore, multiple gaps or cells must be measured to provide an assessment of mean velocity in the capillaries. The capillary diameters are too small to be measured and so the flow in the vessels cannot be estimated from these velocities. It is also uncertain whether the rate of flow of the leucocytes which may stick to the endothelium of the capillaries, particularly in disease processes, is the same as the erythrocytes or plasma.

The pattern of flow in the choriocapillaris has been observed by using videoangiography and intravenous injection of indocyanine green.¹⁹ This requires video recordings of 15 or 30 frames per second and digital subtraction of sequential frames to show the change in fluorescence in the blood vessels of the choroid. The rate of change of fluorescence in the choriocapillaris is faster than in the underlying blood vessels so that the images produced primarily show the changes in the capillaries.

Many studies examining the blood flow in the retinal circulation have been performed with bidirectional laser Doppler velocimetry (BLDV) which measures the velocity of blood in the intraocular retinal circulation by detecting the frequency shifts in laser light caused by the flow of erythrocytes.²⁰ The Doppler principle is applied – that is, the change in frequency of waveform is proportional to the velocity of the object. Often the results are averaged over measurement times of a few seconds to provide mean blood velocity. The measurement of the diameter of retinal arterioles or venules from monochromatic fundus photo-

graphs thereafter allows estimation of the blood flow from the formula:

$$\text{blood flow} = \frac{\pi \times \text{diameter}^2}{4} \times \text{mean velocity}$$

Estimation of total retinal volumetric flow in this way requires measurements of each major branch of the central retinal artery and vein. Although estimation from one branch alone may correlate well with total retinal blood flow in healthy subjects this is unlikely to be the case in disease where areas of the retina are often disparately affected. Reproducibility from the retinal arterioles is poorer than from the venules, probably because the short examination interval of a few seconds results in error from the pulsatility of the arteriolar blood flow. The technique may be difficult to perform because of a susceptibility to error from saccadic eye movements and requires specialised equipment which has confined its use so far to the research laboratory. Recently, laser Doppler velocimetry has also been applied to the measurement of choroidal²¹ and optic nerve head blood flow²² in animals.

Another method employing laser light to estimate retinal blood flow is the laser speckle phenomenon.^{23,24} The scatter of laser light caused by movement of an object is proportional to the velocity of the object. Measurement of the scatter from a retinal vessel allows an estimation of the velocity of the blood cells in the vessel. This technique may be useful for the estimation of capillary flow but as yet has not been extensively investigated.

Any determination of blood flow by visualisation of the retina – for example, by fluorescein angiography, BLDV, or laser speckle phenomenon requires the use of mydriatics in most circumstances. These agents by their sympathomimetic or anticholinergic actions may affect blood flow. In addition, any system which requires the measurement of the diameter of retinal blood vessels requires adjustment of those measurements for the refractive error, axial length, or keratometry of the eye. Correction factors have been devised by Littman^{25,26} and Bengtson²⁷ but their accuracy has recently been questioned.²⁸ If serial measurements are being used and absolute blood flow values are not required then a measurement of the distance between the disc and the fovea may be used to standardise the magnification of photographs of the same individual.²⁹ The use of light to examine the retina can also affect the blood flow which may vary after short durations of retinal illumination and dark adaptation.³⁰

Blood velocities in the macular capillaries have been assessed by non-optical means using the blue field entoptic phenomenon, appreciable if we look at a deep blue sky.^{31,32} This method presents a diffuse blue light (430 nm) to one eye of a subject allowing visualisation of his or her own white blood cells in the macular capillaries (seen as multiple white 'comma'-shaped flecks momentarily crossing the paracentral visual field). The density and velocity of these are matched by the subject to the density and velocity of spots on a VDU screen which is observed simultaneously with the other eye. The system therefore requires the cooperation of the subject, good vision in the eyes, and introduces an unavoidable subjective component.

A number of methods have been devised for the estimation of the pulsatile component of total ocular blood flow from the variations that occur in intraocular pressure with the systemic pulse.^{33,34} These variations in pressure can be measured by tonography (Fig 2) and have been related to volume changes in cadaver eyes allowing extrapolation of the intraocular pressure changes to variations in blood volume with the systemic pulse. Such an extrapolation may, however, be inaccurate when the size of the eye or the ocular rigidity is changed – for example, in myopia.^{34,35} Several assumptions which must be applied with these techniques have been

Figure 2 A tonography tracing is shown, illustrating the variations in the intraocular pressure from which the pulsatile flow in the left eye (mostly choroidal) can be estimated.

outlined^{33,36}: (1) The change in intraocular pressure is related to the change in volume induced by the flow of blood into the eye with each pulse; (2) retrograde blood flow does not occur; (3) the outflow of blood is constant and non-pulsatile; (4) the formulas for the calculation of pulsatile blood flow from the pressure changes are valid; (5) the blood vessels do not collapse.³⁷ Furthermore, pulsitometry measurements only detect the pulsatile component of blood flow, the non-pulsatile component is not measured. The relation between pulsatile and total blood flow is unclear.

In oculo-oscillo-dynamography a tonometer and suction cups are applied to the sclera of the eye.³⁸ The intraocular pressure is raised and changes in the waveform from tonometry are interpreted to indicate cessation of flow in the retinal and choroidal vasculature allowing, it is claimed, measurements of retinal and choroidal pulse pressure. The rise in intraocular pressure results in the undesirable side effect of obscuration of vision when systolic retinal blood pressure is reached. The use of the sclera suction cup also introduces an invasive component which may induce unphysiological circumstances such as ischaemia on the eye which may alter its blood flow. The effect of the suction cup in raising intraocular pressure may be altered by the size of the eye as has been shown to occur with ocular pneumoplethysmography, a similar technique employing a pneumatic tonometer.³⁹

More recently colour Doppler ultrasound imaging has been used to examine the pulsatile blood velocity profiles in various blood vessels in the orbit including the ophthalmic artery, central retinal artery and vein, posterior ciliary arteries, and the orbital veins.⁴⁰⁻⁴² This technique employs simultaneous B scan and Doppler imaging (with Doppler frequency shifts encoded as coloured pixels on a VDU B scan image) to allow the location and identification of blood vessels. The use of the Doppler equation to convert the Doppler frequency shifts to velocity values requires that the direction of travel of the blood vessel is known and the calculations of blood velocity adjusted accordingly, otherwise errors in the velocity calculations occur. This can be done in the two dimensional plane of the scan if a portion of the blood vessel can be seen. It is usually possible to determine the direction of travel of the

straighter blood vessels such as the central retinal vessels in the optic nerve and the ophthalmic artery but is more difficult for tortuous vessels such as the posterior ciliary arteries.

The system has the advantage of measuring a spectrum of blood velocities (Fig 3) in vessels which are not visible by optical methods, but as yet the resolution of the ultrasound does not allow measurement of the diameters of these vessels. Any extrapolation of the blood velocities to blood flow must be performed with care in case undetected changes in the calibre of the vessels occur. The pulsatile component of the blood velocities can be measured by calculating various indices from the velocities, allowing estimations of the resistance to blood flow in the circulation under study.

Blood flow in the normal eye

Total human ocular blood flow is estimated to be approximately 1 ml/min, most of which supplies the vasculature of the uvea (primarily the choroid), only 2-5% supplying the retina.⁴³ The eye is supplied by the ophthalmic artery; in this vessel blood pressure is estimated to be two thirds of brachial blood pressure. The perfusion pressure of the eye is, however, less than this because the intraocular pressure is 10 to 21 mm Hg. A formula has been used to estimate mean ocular perfusion pressure:

$$\text{mean OPP} = 2/3 (\text{DBP} + 1/3 (\text{SBP} - \text{DBP})) - \text{IOP}$$

where OPP=ocular perfusion pressure, DBP=diastolic blood pressure (brachial); SBP=systolic blood pressure (brachial); IOP=intraocular pressure.

The blood flow to the eye is pulsatile and induces intraocular pressure variations from which the mean pulsatile component of the blood flow to the eye has been estimated at approximately 0.724 ml/min.³⁴

In the human, the retinal circulation has a mean flow of 0.033 ml/min.²⁰ In the retinal arterioles blood flow probably exhibits a shearing core with blood flowing at a uniform rate centrally and more slowly peripherally and conforms to the principles of an end artery system with equal flow in the retinal arterioles and venules.⁴³ Blood velocities in the retinal circulation are pulsatile both in the central retinal artery and the vein.⁴⁴ Regional differences in the retina exist with higher flow in the vasculature of the temporal region than the nasal region, reflecting the increased retinal area supplied by the temporal vessels and the increased metabolic activity of the macula.⁴³ The mean blood velocity in the arterioles is higher than in the venules because the diameter of the intraocular retinal arterioles is less than the retinal venules. In the retina autoregulation of blood flow exists, probably a local response of the vessels to metabolites from the retinal cells. The role of the autonomic nervous system is uncertain, for although autonomic receptors have been detected in the retinal blood vessels in their extraocular course, they are thought to be absent from the intraocular retinal circulation.⁴⁵

Figure 3 A spectral analysis of the blood velocities in the ophthalmic artery from the colour Doppler examination of a healthy volunteer is provided.

In the uveal tissues autonomic receptors are present and blood flow can be altered by manipulation of the autonomic system – for example, stimulation of the sympathetic system reduces blood flow whereas cervical sympathectomy causes an increase in flow.⁴⁶ In contrast with the retinal circulation autoregulation of blood flow probably does not occur in the choroid, possibly because the choriocapillaris separates the choroidal arterioles and venules from the retina and therefore from its metabolites.⁴⁵ The high blood flow and low utilisation of nutritive substrates in this circulation may also reduce the effect of retinal metabolism. The difference in the responses of the retinal and choroidal circulations is evident when ocular perfusion pressure is reduced, resulting in reduced choroidal blood flow while retinal blood flow remains stable.⁴⁵ The choriocapillaris fills first at the macula and then in the periphery.¹⁹

Blood flow in the eye can be affected by both systemic and ocular factors. Changes in posture should be expected to alter the perfusion pressure in the ophthalmic artery pulse pressure but this varies only by 10 mm Hg or less when standing.³⁴ The confusing relation of pulsatile blood flow in the eye to total blood flow is highlighted by the reduction in pulsatile blood flow of 27.5% on the assumption of the supine position in healthy volunteers despite a rise in the perfusion pressure.⁴⁷ Retinal blood velocities are stable during postural changes despite alterations in perfusion pressure^{42,48} and flow is effectively autoregulated during increased systemic blood pressure from isometric exercise until mean brachial artery blood pressures reach 115 mm Hg after which the blood flow increases.⁴⁹ Evidence that autoregulation in the retinal circulation is controlled by metabolites has been provided by the observed responses to hyperoxia or hypercapnia.⁵⁰ In one study, retinal arteriolar vasoconstriction and venular dilatation were observed after high concentration oxygen breathing but no change was detected with variation of blood carbon dioxide levels.³⁰ Dilatation of the retinal blood vessels and shortening of fluorescein dye transit times have, however, been detected in monkeys with increasing arterial partial pressure of carbon dioxide,⁵¹ and more recently in humans.⁵⁰ In the macular circulation during isocapnic hypoxia blood velocities have been found to increase by 38% (the diameter of the arterioles and the venules increased by 8.2% and 7.4%, respectively), whereas hyperoxia reduced the velocity by 36% (the diameter of arterioles and the venules reduced by 5.6% and 10% respectively).⁵² These variations were unexpectedly large considering the small rise in blood oxygen content that can be induced by hyperoxia (oxygenised haemoglobin does not rise significantly). In recent studies performed with scanning laser ophthalmoscopy, changes in blood velocity (10% variation) were found to be more in keeping with the expected changes associated with isocapnic hyperoxia and hypoxia.⁵⁰ The changes in the diameter of the larger retinal vessels are believed to be too small to account for the changes in blood flow seen with such alterations in oxygen concentration.⁵³ As elsewhere in the body, it is postulated that the smaller retinal arterioles and venules contribute most to the regulation of blood flow.

Raised intraocular pressure causes a reduction in blood flow to the anterior uvea, choroid, and retina.² The retinal blood flow is however autoregulated up to intraocular pressures of 30–34 mm Hg after which the perfusion decreases while intraocular pressures lower than 10 mm Hg cause the retinal blood flow to increase.^{2,53} With high intraocular pressures the perfusion of the eye continues until the pressure reaches 6 mm Hg below the perfusion pressure of the blood in the ophthalmic circulation, at which point the critical closing pressure of the ocular vascular bed is reached and blood flow ceases.⁵⁴

The effect of illumination of the retina has been investigated by a number of techniques. In animal models, flicker-

ing light increases the retinal blood flow whereas constant illumination reduces retinal blood flow.⁴⁵ In humans increases of 65% in retinal blood velocity, 5% in venular diameter, and 82% in calculated blood flow rate have been reported in the first seconds after dark exposure⁵⁵ with peak measurements reached after 5 minutes of dark adaptation when the velocity in the venules was 47% higher than light adapted levels. In another study of the retinal arterioles increases in blood velocity of 40–55% were detected with negligible dilatation of the arterioles of 2–3% and increases in the calculated flow rate of 40–70%.⁵⁵ In contrast, no change in blood flow in the choroid with dark adaptation was found using infrared absorption cineangiography with indocyanine green.³⁰ Measuring the response of the retinal blood flow to dark adaptation may provide a means of assessing the autoregulatory capacity of the retina and may be used in the investigation of conditions such as diabetes.

Blood flow measurements in ocular pharmacology

A number of topical and systemic medications may influence the blood flow to the eye and have particular relevance, therefore, to different disease processes such as diabetes, glaucoma, systemic hypertension, and ocular vascular occlusion. β Blockers and sympathomimetics may affect blood flow because an imbalance is produced between the influence of the α and β sympathetic receptors on the ocular vasculature. The effect of this imbalance has often been difficult to ascertain and differing results have been found in various studies. Even though these agents can affect various measurements which are relevant to blood flow it is often difficult to determine whether these effects are beneficial or detrimental to the eye. The effects of the agents upon systemic blood pressure, intraocular pressure, and the untreated fellow eye often confound the interpretation of the results. For example, the contralateral eye has often been used to apply placebo drops; this, however, does not take into account the systemic absorption of the active agent nor the interrelation which may exist between eyes for the control of intraocular pressure.

The imbalance of sympathetic stimulation induced by medications may cause changes in blood vessel calibre. Indeed vasoconstriction has been detected in the ocular circulations with both sympathomimetics and β blockers. For example, vasoconstriction was produced in the ciliary body after instillation of topical phenylephrine hydrochloride, timolol maleate, and betaxolol hydrochloride into rabbit eyes.⁵⁶ Tolerance developed to betaxolol and partially to phenylephrine after 7 weeks of administration of the drugs. In humans, Martin and Rabineau detected vasoconstriction of the retinal arterioles with timolol in serial examinations of monochromatic fundus photographs.²⁹ It is the expectation that vasoconstriction will decrease flow. This has occurred with the use of adrenaline which has produced a reduction of blood flow to the iris and ciliary processes of rabbits⁵⁷ and in monkeys⁴ in investigations using microsphere techniques. With β blockers often no changes in blood flow have been detected. For example, a crossover study using a single instillation of timolol, betaxolol, and levobunolol in normal subjects failed to find any changes in perimacular haemodynamics (measured by blue field entoptic simulation) in normal subjects compared with a placebo condition.⁵⁸ Similarly, Green using radioactively labelled microspheres to examine topical therapy on rabbit eyes found no effect on blood flow with timolol (nor with noradrenaline, ecthiopate iodide, or pilocarpine).⁵⁷ Studies employing tonography have shown no effect of timolol on pulsatile ocular blood flow in normal individuals⁵⁹ and in patients with glaucoma⁶⁰ and Grunwald has detected no effect of carteolol on blood velocity, volumetric flow rate, or venous diameter in the retinal circulation using laser Doppler velocimetry.⁵⁵ Another

study using the latter method, however, detected an 11% increase in the maximum velocity of red blood cells in the retina and 13.2% of estimated blood flow in timolol treated eyes⁶¹ and a similar effect has been found in patients with ocular hypertension.⁶² Using colour Doppler imaging topical timolol had no effect on blood velocities in the ophthalmic artery or central retinal arteries but produced a reduction in the mean resistive indices in the treated eye and contralateral untreated eyes, perhaps signifying reduced peripheral resistance to flow.⁴²

If agents which lower intraocular pressure, such as β blockers, cause vasoconstriction this may be a response to lowered intraocular pressure and not a direct effect of the drug on the blood vessels. Vasoconstriction may occur to compensate for the increased perfusion pressure resulting from lowered intraocular pressure, thereby stabilising the blood flow. Studies employing techniques which can estimate the blood pressure in the ocular vessels have not always detected such changes in perfusion pressure. For example, using compression ophthalmodynamometry, although mean blood pressure in the ophthalmic artery was increased in timolol treated eyes compared with the 'placebo treated' contralateral eye, multiple other variables, such as diastolic and systolic blood pressure and serial measurements of blood pressure in the ophthalmic artery were unchanged.⁶³ Pullinatt and Stodtmeister, in a parallel comparison of normal individuals using oculo-oscillo-dynamography, found no change in retinal or ciliary perfusion pressures with timolol, betaxolol, pilocarpine, and acetazolamide despite reductions in intraocular pressure.⁶⁴ Carteolol even produced a significant reduction in perfusion pressure in this study.

The topical application of the α agonist aproclonidine which might be expected to cause vasoconstriction has produced no acute effects on macular blood flow on blue field simulation in normal subjects after single dose topical administration.⁶⁵ Colour Doppler imaging, however, in the same study detected a reduction in the end diastolic velocities from the posterior ciliary circulation suggesting reduced peripheral resistance to flow.

Intravenous acetazolamide has been shown to cause vasodilatation and increase retinal blood velocities (laser Doppler velocimetry) in normal volunteers.⁶⁶ A carbonic anhydrase inhibitor, this agent causes an increase in tissue partial pressure of carbon dioxide which may have induced vasodilatation of the retinal vessels. In combination with the increased perfusion pressure from reduced intraocular pressure and the measurement of increased blood velocities it would appear highly likely that increased blood flow occurs with the drug. This may be usefully exploited to increase blood flow in conditions such as central retinal artery occlusion.

The effects of other agents have been investigated primarily in experimental circumstances using animal models. For example, dopamine antagonists have been shown to increase pulsatile blood flow in the eyes of rabbits while reducing intraocular pressure.¹⁹ In the same study dopamine and bromocriptine had no effect on flow. Anticholinesterase inhibitors have reduced the flow detected in the anterior uvea in rabbits (microspheres method).⁶⁷ Further investigations of the effects of drugs may be stimulated by recent investigations of the effects on the ocular circulations of endothelin-1 and nitric oxide which are derived from vascular endothelial cells, the former causing vasoconstriction and the latter vasodilatation.^{68,69}

Although considerable efforts have been made to examine the potential effects of drugs on ocular blood flow the clinical relevance of the findings is as yet unclear, particularly with topical medications such as β blockers. Studies should be examined carefully for methodology before the conclusions are accepted.

Blood flow and ocular disease

Ocular and systemic diseases have been investigated using various techniques for examination of ocular blood flow but few are applied in the clinical setting. There are, however, diseases in which the measurement of blood flow might aid diagnosis and management.

In diabetic retinopathy retinal blood flow may be reduced and the normal autoregulatory capacity be deficient.^{3,70} Small induced diabetes in dogs and noted that retinal blood flow was significantly reduced after 5 months, using a radionuclide labelled microsphere technique.³ Grunwald, using laser Doppler velocimetry, investigated diabetic patients with poorly controlled blood glucose and, in comparison with normals, found that the autoregulatory response to oxygen breathing (that is, decreased retinal blood flow) was less in diabetic patients.⁷⁰ A mean 15% increase in retinal blood flow during hyperglycaemia compared with normoglycaemia (after administration of insulin) was found in poorly controlled type 2 diabetic patients examined by laser Doppler velocimetry.⁷¹ The autoregulatory response to oxygen breathing was reduced during hyperglycaemia in these patients. A reduction in mean retinal venous diameter, red blood cell velocity, and volumetric blood flow (from laser Doppler velocimetry) has been detected after panretinal photocoagulation with a return of the autoregulatory response to oxygen breathing.^{72,73} Reduced choroidal blood flow in diabetic patients has been suggested by the observation of a mean pulsatile ophthalmic artery blood flow (from ophthalmodynamometry) of only 0.15 ml/min.³⁴ It therefore appears that blood flow in the eye may be reduced in patients with diabetic retinopathy particularly in the retinal circulation. Those with poor control may have a relative increase in blood flow which is then reduced by tightening glucose management. Whether clinically applicable methods of blood flow assessment can be used to monitor the progress of diabetic retinopathy and responses to treatment remains to be seen.

Ocular haemodynamics are altered in patients with glaucoma and ocular hypertension but the methods of studies must be examined to ensure that topical medications have been stopped (because of their potential effects on blood flow) with adequate washout periods employed. Of course, if the patient is off treatment, blood flow changes may merely reflect the presence of raised intraocular pressure and not primary vascular abnormalities. With these caveats in mind, studies of patients with chronic open angle glaucoma have found prolonged dye transit times on fluorescein videoangiography^{74,75} and reduced ophthalmic artery velocities by duplex Doppler ultrasound⁷⁶ and colour Doppler imaging.⁷⁷ More severe loss of visual function in glaucoma has been associated with reduced white blood cell velocities in the macula (and presumably reduced macular blood flow) using blue field simulation.⁷⁸ After treatment by trabeculectomy increased blood velocities and evidence of reduced peripheral resistance to flow have been detected in the central retinal artery and posterior ciliary arteries by colour Doppler imaging.⁷⁹ The alterations in blood flow were most likely to have resulted from the intraocular pressure drop from the operation but the measurements may also have been influenced by the fact that most of the patients were on topical medications such as β blockers preoperatively but not postoperatively.

To avoid the problem of raised intraocular pressure Trew compared the results of ophthalmodynamometry in patients with ocular hypertension with patients having primary open angle glaucoma.⁴⁷ The patients with glaucoma had a lower mean pulsatile ocular blood flow.⁶⁰ Obviously patients with normal tension glaucoma do not have the confounding influence of raised intraocular pressure. A study of such patients using colour Doppler imaging found increased vascular resistance in the ophthalmic arteries when compared

with age-matched healthy control subjects.⁸⁰ The increased resistance was normalised when partial pressures of carbon dioxide were elevated in the patients suggesting the presence of reversible vasospasm in these patients with normal tension glaucoma. Reduced pulsatile blood flow from ophthalmodynamometry has also been detected in such patients.⁸¹ Whether the reduced blood flow in glaucoma is contributing to the pathogenesis of the disease or is secondary to the loss of nerve fibres in the disease remains as yet undetermined.⁸²

Cranial arteritis (often a clinically hazardous condition to manage) can cause profound haemodynamic changes in the orbit. Intraocular pulse pressure amplitude (the measure from which ophthalmodynamometry estimations of pulsatile blood flow are obtained) has been compared in patients with giant cell arteritis and patients with non-arteritic anterior ischaemic optic neuropathy or non-arteritic central retinal artery occlusion.⁸³ The arteritic patients showed a mean pulse amplitude which was only 37% of the mean value in the non-arteritic group (estimated values of pulsatile ocular blood flow of less than 0.6 ml/min in the arteritic group). In another study using a pneumotonometer the mean ocular pulse amplitude was reduced in patients with ischaemic optic neuropathy and temporal arteritis but not in those with neuropathy alone or temporal arteritis alone.⁸⁴ In this group patients with ischaemic optic neuropathy and central retinal artery occlusion associated with temporal arteritis also showed a reduced pulse amplitude in their contralateral eyes. Many of these patients' recordings increased after treatment with prednisolone. Colour Doppler imaging has also been used to demonstrate occlusion of the orbital vessels in ischaemic optic neuropathy and central retinal artery occlusion⁸⁵ and has been used to detect extensive occlusion of the vessels in temporal arteritis and an increase in blood velocities after treatment.^{86, 87} In temporal arteritis the severity of the disease appears to be associated with more severe changes in blood flow, therefore monitoring of blood flow should aid diagnosis and the determination of the response to therapy.

In central retinal vein occlusion blood flow has been shown to be reduced by fluorescein angiographic techniques^{88, 89} and more recently by colour Doppler imaging.^{90, 91} The development of retinal ischaemia appears to be related to the reduction in the blood flow at onset showing that there is a graduation in the severity of the occlusive process. In a recent study, blood flow was reduced particularly in the first 3 months after the onset of the occlusion and the severity of the reduction in flow in the central retinal vein (a minimum venous velocity of less than 3.0 cm/s) could be used to predict the development of iris neovascularisation more accurately than observation of retinal ischaemia on fundus fluorescein angiography.

Stenosis of the carotid arteries sometimes reduces the ocular blood flow although studies have revealed differing results.^{94, 92, 93} Using colour Doppler imaging the location of the occlusion associated with carotid disease has been facilitated. For example, occlusions have often been detected at the level of the ophthalmic artery potentially altering the decision for carotid surgery.⁹⁴⁻⁹⁶

Reduced pulsatile ocular blood flow has also been found in cataractous patients, the relevance of which is unknown.⁹⁷

Conclusion

The measurement of blood flow in the eye is a complex and often confusing issue. No technique has reached the status of a standard and all have disadvantages not least because of their measurement usually of only one of the many variables involved in blood flow. Their collective application over many studies, however, has revealed patterns of haemodynamic change in normal physiology and in ocular diseases. As the technology and its application continue to improve,

the shortfalls of current methods are gradually met. In the future, more of these methods may be available to the physician in the clinical setting.

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