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Methods for Determination of Optic Nerve Blood Flow*

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A variety of studies have been conducted over the past two decades to determine if decreased optic nerve blood flow has a role in the etiology of glaucomatous nerve damage. Five basic methods have been employed in examining blood flow. Invasive studies, utilizing electrodes placed in the optic nerve head, represent one of the first attempts to measure blood flow. More recently, the methodologies have included axoplasmic flow analysis, microspheres, radioactive tracers such as iodoantipyrine, and laser doppler measurements. The results of these studies are inconclusive and frequently contradictory. When the studies are grouped by methodology, only the iodoantipyrine data are consistent. While each of the experimental techniques has limitations, iodoantipyrine appears to have better resolution than either invasive studies or microspheres.

INTRODUCTION

Glaucoma refers to a group of diseases in which elevated intraocular pressure causes optic nerve damage and visual field loss. Glaucoma is one of the leading etiologies of blinding eye disease. The incidence of glaucoma in people over 40 is estimated at 1.5 percent [1].

The pathogenesis of glaucomatous optic nerve damage is unknown. There are two widely accepted hypotheses regarding the mechanism of optic atrophy in glaucoma. As early as the 1850s, Muller proposed that mechanical compression of the optic nerve fibers induced by high intraocular pressure was directly responsible for injury and death of the neurons [2]. In 1858, von Jaeger argued that increased intraocular pressure led to neuronal damage through ischemia and not through a compression of the nerve fibers [3].

The argument over which of these two theories is correct remains an open question and a much-debated topic 130 years later. Various proponents of each theory have stressed the evidence in support of their own view while minimizing other data. For example, Hayreh states, "It can be said that the available evidence strongly suggests that in PAOG [primary open angle glaucoma] and LTG [low tension glaucoma] ... visual field defects are due to vascular disturbances in the anterior part of the optic nerve. The crusaders against the vasogenic theory have not provided any definite proof of the mechanical theory ... " [4]. Yet Maumenee, in direct contradiction to Hayreh's article, argues, " ... There is no evidence in the physiologic experiments that have been done to date, nor in the histologic studies performed on human eyes with glaucoma, to indicate that vascular alteration ... is the primary factor in axonal damage and visual field loss" [5].

Abbreviations: CNS: central nervous system IOP: intraocular pressure LDF: laser doppler flowmetry LTG: low tension glaucoma ONH: optic nerve head POAG: primary open angle glaucoma

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There are several factors contributing to these divergent theories of pathogenesis of optic nerve damage in glaucoma. While many investigators have studied the relationship between intraocular pressure and optic nerve perfusion, the eye presents obstacles to accurate measurement of blood flow. Small volume of flow, size, error introduced with manipulation, and inaccessibility of the vasculature represent some of the unique technical problems in analysis. Methods for estimating blood flow in other vascular beds frequently yield unsatisfactory measurements when confined to the retina or optic nerve [6]. Given the difficulty in accurately quantifying optic nerve blood flow and given the wide variety of methods employed in blood flow analysis, it is not surprising that the etiology of nerve damage in glaucoma is unclear.

INVASIVE METHODS OF BLOOD FLOW MEASUREMENT

Various electrodes placed directly on the optic disk represent one of the first attempts to measure blood flow accurately. Ernest and Potts developed a thermocouple probe to measure temperature change on the surface of the optic nerves of cats. Elevations in intraocular pressure (IOP) that were similar to the pressures found in open angle glaucoma decreased optic disk temperature, suggesting a decrease in blood flow [7]. Ernest later measured optic disk oxygen tensions in cats with a micro-oxygen probe. He found changes in systemic blood pressure did not alter optic disk oxygen tensions after an initial period of equilibration [8].

In 1976, Ernest attempted to measure blood flow over a range of intraocular pressures with the microelectrode hydrogen clearance method. Using 12 rhesus monkeys, he found little change in blood flow to the optic nerve until IOP was elevated to levels much greater than clinical relevancy. Ernest concluded that there is an efficient autoregulation of blood flow to the optic nerve similar to that found in the cerebral or retinal circulation [9]. Armaly and Araki conducted two studies where blood flow was measured 2–4 mm behind the globe in the optic nerve. Using the heated thermocouple technique, they found flow to the nerve was stable until intraocular pressure exceeded 50 mm Hg, outside the range commonly found in primary open angle glaucoma [10,11].

While the invasive studies directly measuring blood flow give relatively consistent results, the methodologies warrant criticism. An inherent weakness of these studies is the effect insertion of the electrode has on blood flow. Ernest has stated that the reinsertion of the electrode with each alteration in IOP may have had an effect on flow [9]. Noninvasive methods with little ocular manipulation would eliminate the error introduced by these studies.

Finally, two of the above authors used cats to carry out their studies [7,8]. Evidence indicates that optic nerve blood flow results obtained from cats have limited applicability to humans. Hayreh argues that the blood supply to the optic nerve in cats is different from that in humans since cats have no internal carotid artery, no opthalmic artery, and no central retinal artery, and the nerve is perfused from a branch of the external carotid [12]. The different vascular supply of the eye in the two species makes it difficult to extrapolate blood flow results from cats to humans.

AXONAL TRANSPORT AND BLOOD FLOW

Many investigators have found that increased intraocular pressure appears to block axonal transport in the optic nerve where it passes through the lamina cribrosa, a sievelike structure in the sclera [13–19]. Both the mechanical damage theory and the

decreased perfusion theory can be invoked to explain this phenomenon. The blockage of axonal transport could be the result of ischemia from high IOP since blood flow is necessary to provide nutrients and oxygen for this energy-dependent process [20]. The mechanical effect of increased IOP producing distortion and compression of axons could be an equally plausible alternative for explaining impaired axonal transport [21,22].

Two studies of axonal transport indirectly examined blood flow and arrived at contradictory conclusions. Sossi and Anderson reported that blockade of axonal transport by high IOP in the cat was influenced by cardiovascular factors such as blood pressure. They concluded that ischemia must have a role in the blockade of fast axonal transport [23]. Minckler examined axoplasmic flow in *Macaca fascicularis*. He found elevation of PO_2 did not reverse IOP blockade of axonal transport. Perfusion with avian erythrocytes indicated that nerve head circulation was intact. Minckler's results were not consistent with tissue hypoxia causing blockade of axonal transport [24].

Direct objections can be raised to the methods employed in each of these studies. Sossi and Anderson used a cat model in their experiments, but the histology of the cat lamina cribrosa is different from the structure of the lamina cribrosa in man [25]. Minckler's evidence for intact perfusion in optic nerve heads over a range of IOP was the patency of the vessels to nucleated avian erythrocytes. Patency, however, does not imply adequate flow since these techniques cannot measure actual perfusion. Furthermore, capillaries are more resistant to ischemic damage than either glial or nervous tissue. Capillaries could remain intact while axons are dying from decreased perfusion [26].

MICROSPHERIC ANALYSIS OF BLOOD FLOW

When Rudolph and Heyman introduced the radioactive microsphere technique to measure *in vivo* fetal blood flow, it represented a significant improvement over invasive methods because no manipulation of the vascular bed was involved [27]. The technique became popular for measuring regional blood flow and was subsequently employed by many investigators to measure perfusion of the optic nerve.

There are a number of theoretical considerations which influence the resolution of labeled and unlabeled microspheres. For accurate measurements of blood flow, there must be adequate mixing of the microspheres so that there is a uniform concentration in arterial blood. The microspheres are trapped in the capillaries of a given tissue in proportion to the blood flow to that tissue. In tissues of relatively small volume of perfusion, the number of microspheres trapped must be large enough to insure an adequate determination of flow [28].

Critics of the microsphere technique raise three primary objections. The microspheres may obstruct arterioles, thus altering blood flow; they have a tendency for axial streaming; and there may be insufficient numbers of microspheres to count [29]. Wallin found a significant amount of axial streaming in the 15 μm microspheres, which led to errors of as much as 100 percent [30]. Inaccuracy in measuring blood flow was further increased when blood flow was studied with larger microspheres [31].

Despite the limitations of microspheres, their ability to evaluate regional perfusion with reproducible results has led to five studies of optic nerve flow. Alm and Bill examined the effect of increased intraocular pressure on optic nerve flow in cynomolgus monkeys. Using 15 μm diameter microspheres, they found moderate increases in IOP caused reductions in blood flow to the prelaminar region of the optic nerve. The

number of spheres trapped in the nerve head was too low to allow accurate determinations. Furthermore, when a larger dose of microspheres was injected, the blood pressure of the monkeys rose significantly [32].

Bill attempted to correct some of the methodologic problems of his previous experiments when he used 8 to 10 μm microspheres. A greater number of smaller spheres could be injected without altering blood flow. Bill and Geijer found perfusion throughout the optic nerve to be stable over a wide range of IOP, although there was a slight decrease in flow with increased IOP [33].

Bill's study illustrates one of the recurring problems in blood flow analysis, a problem common to the invasive methods of Ernest and others. While Bill and Geijer found only a slight decrease in blood flow with increased intraocular pressure, the resolution of the microsphere technique was unable to ascertain whether the reduction in flow was homogeneous. A small decrease in perfusion could lead to a focal area of ischemia if the distribution of the decrease was not uniform. Bill and Geijer concluded that new methods of analysis need to be developed so that small regions of nerve can be studied for ischemia.

Weinstein and co-workers, using 15 μm radioactive microspheres in sheep, found that blood flow to the optic nerve was stable over a wide range of blood pressures [34]. In later studies, Jay examined the effects of digital massage and applied pressure to the eye on blood flow. Employing 15 μm microspheres in a rabbit model, Jay et al. found that optic nerve perfusion increased following release of applied pressure and drop in IOP [35,36].

While these studies are more recent than Bill's pioneering work, many of the same criticisms apply. Sheep and rabbits do not allow one to extrapolate to humans because of the different vascular supply of the nerve head. Microspheres 15 μm in diameter are subject to axial streaming, causing large inaccuracies. Intraocular pressure in Jay's study was only temporarily increased. Finally, small areas of ischemia are beyond the resolution of microspheres, and the technique gives information about blood flow for only a short period of time.

RADIOACTIVE TRACER METHODS IN BLOOD FLOW ANALYSIS

Radioactive tracers have been used to measure central nervous system blood flow for the past two decades [37]. Originally, investigators used an iodine-131 labeled inert gas, trifluoroiodomethane, for determination of a focal perfusion in brain. The trifluoroiodomethane technique depended on uptake of the tracer by various brain tissues. The more blood flow to a given area, the more tracer would be deposited in the tissue, and the darker the area would appear on an autoradiograph.

While trifluoroiodomethane represented an accurate technique for measuring local central nervous system (CNS) blood perfusion, it was difficult to use. The tracer was not commercially available, it had a short half-life, and analysis of a gaseous tracer in tissue by autoradiography presented technical problems [38]. A non-volatile tracer was subsequently sought.

In 1976, Kollarits examined blood flow to the optic nerve and retina in rhesus monkeys with C14-antipyrine. Antipyrine was not volatile, it had a longer half-life than the methane gas, and the C14 label allowed for improved resolution over iodine-131. Blood flow to the optic nerve measured with antipyrine was similar to values obtained with microspheres [39].

Other studies indicated C14-antipyrine was less than optimal for blood flow

calculation. Values of cerebral blood flow were considerably less than those obtained with labeled inert gases. Uptake of antipyrine by CNS tissues was too small for accurate determination of local perfusion. In highly perfused tissues, the method led to large underestimates of blood flow [40].

In 1979, Sakurada and co-workers introduced an analogue of antipyrine, C14-iodoantipyrine, as a new tracer for blood flow analysis. Iodoantipyrine was more lipophilic than antiyprine, it had an improved ability to diffuse through the blood-brain barrier, and it was degraded at a slow rate. Local cerebral blood flow was determined more accurately with iodoantipyrine than with antipyrine [41].

While microspheres may obstruct vessels, altering perfusion, such methodological difficulties do not apply to iodoantipyrine because of its small size. Unlike the invasive studies, electrodes do not have to be continually reinserted into the optic nerve head. Even in areas of low volume of flow, iodoantipyrine retains a high degree of resolution [42].

To date, two studies have employed the C14-iodoantipyrine technique in optic nerve blood flow analysis. Sossi and Anderson studied the effects of alterations in intraocular pressure on nerve and choroidal blood flow [43]. Sossi and Anderson concluded that increased intraocular pressure did not decrease blood flow, while Weinstein found no relationship between blood pressure from 60–120 mm Hg and nerve perfusion.

Since both of these studies used a cat model for analysis, their applicability to humans is arguable. Diffusion of C14-iodoantipyrine also presents methodologic problems. The tracer may diffuse from a zone of high flow to a zone of low flow. Such diffusion might obscure a small area of ischemia in the lamina cribrosa or elsewhere. Hayreh contends that the iodoantipyrine technique gives "more information on diffusion than on blood flow in the ONH [optic nerve head]" [44].

According to Sossi and Anderson, evidence from their study indicates that diffusion of iodoantipyrine is not significant. They point to a sharp boundary, less than 70 μm, which occurs between the non-vascularized vitreous and the optic nerve head. The investigators claim that such a sharp boundary indicates diffusion of tracer occurs over a region smaller than the lamina cribrosa [43].

Given the high aqueous content of the vitreous humor [45], and given the hydrophobic nature of iodoantipyrine, the radioactive tracer would probably not be found in the vitreous even in the presence of significant diffusion. The lipophilicity of iodoantipyrine, making it an ideal tracer for crossing the blood-brain barrier, should give a sharp boundary between two tissues with a differing water content, regardless of the degree of diffusion. Further study of iodoantipyrine's ability to diffuse through unperfused tissues is warranted.

In 1985, Quigley examined optic nerve perfusion with iodoantipyrine autoradiography [46]. His study was unique in several respects. Quigley used tritiated iodoantipyrine instead of C14-iodoantipyrine, he examined short-term and long-term increases in IOP, and his primate model seemed applicable to human glaucoma. Tritium has a number of advantages in blood flow analysis compared to C14. Because the beta particles emitted by tritium are of very low energy, the autoradiographic image is formed from tissue situated less than 5 μm away from the film. As a result, resolution is increased and differences in tissue thickness do not alter the image produced on the autoradiograph [47].

Quigley studied the effects of intraocular pressure on optic nerve head flow. He lasered the trabecular meshwork of macaque monkeys in order to create a long-term

increase in IOP. The neuronal loss in primate laser angle treatment is comparable to neuronal loss in human glaucoma [48–50]. Quigley found no relationship between increased IOP and decreased blood flow. While diffusion of iodoantipyrine was not addressed, more validity can be given to Quigley's results since the vasculature and structure of the optic nerve head in macaque monkeys and humans is similar.

NEW METHODS IN BLOOD FLOW ANALYSIS

Sokoloff developed a technique in the late 1970s for examining glucose consumption in the central nervous system with C14-2-deoxyglucose [51,52]. Sperber and Bill later discovered that occlusion of arterioles in brain resulted in increased uptake of 2-deoxyglucose in focal areas of ischemia [53]. Presumably, the ischemic area was converted from an aerobic to a less energy-efficient anaerobic metabolism, which resulted in increased glucose consumption.

Sperber and Bill then reasoned that the 2-deoxyglucose technique could give an accurate picture of the nutritional status of the optic nerve. If increased IOP resulted in decreased perfusion of part of the nerve, then the metabolism in that region should shift anaerobically with concomitant increase in glucose consumption. Sperber and Bill studied glucose consumption and optic nerve perfusion in monkeys. Employing the C14-2-deoxyglucose technique and microspheres, they found that blood flow and metabolism of the optic nerve is unaltered except at very high intraocular pressures [54].

The deoxyglucose method has a number of theoretical advantages over other methods of measuring blood flow. With microspheres and iodoantipyrine, information about perfusion is only obtained during the period of tracer injection. Data can be obtained for longer periods of time with deoxyglucose. The method gives a high degree of spatial resolution and apparently better resolution than either microspheres or iodoantipyrine, according to Bill [55].

Employing deoxyglucose to study optic nerve flow is not without criticism. Sokoloff originally designed the method to measure glucose consumption in brain. Applying the technique to the eye may not be justified without recalculation of constants for each tissue studied, optic nerve, retina, and so on [55]. Furthermore, decreased perfusion may damage nervous tissue without an anaerobic shift in metabolism of the optic nerve.

Laser doppler analysis represents the latest technique in the measurement of optic nerve blood flow. Laser doppler velocimetry is based upon the doppler effect. The laser light scattered when it strikes a moving red blood cell is shifted by a given frequency [56]. Stern first applied laser doppler velocimetry to blood flow in skin [57]. Riva and co-workers subsequently examined the relationship between red blood cell velocity and intraocular pressure in the optic nerve head. They found red blood cell speed quickly returned to normal after a change in intraocular pressure. Riva concluded that the return to normal of red blood cell speed indicated an autoregulatory response of the optic nerve head vasculature [58].

While laser doppler measurements give quantitative estimates of the speed of red cells in vessels, the signal is linearly related to blood flow. Rundquist studied sciatic nerve blood flow with iodoantipyrine and laser doppler flowmetry. He found an excellent correlation between blood flow as measured by iodoantipyrine and the laser doppler signal [59].

The benefits of laser doppler flowmetry (LDF) over other methods include its

TABLE 1
Optic Nerve Perfusion Studies

Investigator	Method Employed	Animal Model	Result Obtained	Reference
		Invasive Methods		
Ernest and Potts	Thermocouple probe	Cat	Increased IOP, decreased blood flow	[7]
Ernest	Micro-oxygen probe	Cat	Changes in blood pressure with no alteration of disk oxygen tension	[8]
Ernest	Microelectrode hydrogen clearance	Rhesus monkey	Nerve blood flow stable over wide range of IOP	[9]
Armaly and Araki	Heated thermocouple flow	Rhesus monkey	Nerve blood flow stable over wide range of IOP	[10,11]
		Axonal Transport Studies		
Sossi and Anderson	IOP-induced block of axonal transport	Cat	Blood pressure influenced IOP block of axonal transport, suggesting ischemic etiology to blockade	[23]
Minckler et al.	IOP-induced block of axonal transport	Macaca monkey	IOP-induced blockade of axonal transport occurred despite presence of intact capillaries, suggesting mechanical etiology to blockade	[24]
		Microspheres		
Alm and Bill	15 μm labeled microspheres	Cynomolgus monkey	Increased IOP, decreased nerve blood flow	[32]
Geijer and Bill	10 μm unlabeled microspheres	Cynomolgus monkey	Nerve blood flow stable over wide range of IOP	[33]
Weinstein et al.	15 μm labeled microspheres	Sheep	Changes in blood pressure with no alteration of nerve blood flow	[34]
Jay et al.	15 μm labeled microspheres	Rabbit	Nerve blood flow increased after release of applied pressure and drop in IOP	[35,36]
		Radioactive Tracers		
Weinstein et al.	C14-iodoantipyrine	Cat	Changes in blood pressure with no alteration of nerve blood flow	[42]
Sossi and Anderson	C14-iodoantipyrine	Cat	Nerve blood flow stable over wide range of IOP	[43]
Quigley et al.	Tritium-iodoantipyrine	Macaca monkey	Nerve blood flow stable over wide range of IOP	[46]
Sperber and Bill	C14-2-deoxyglucose 10 μm microspheres	Cynomolgus monkey	Nerve blood flow stable over wide range of IOP	[54]
		Laser Doppler Measurements		
Riva et al.	Laser doppler velocimetry	Human	Autoregulatory response of optic nerve blood circulation to increased IOP	[58]

noninvasive nature, rapidity of measurements, continuous recording, and ability to examine small tissue regions [59]. There is one major disadvantage in the application of laser doppler analysis to the optic nerve: the techniques can only measure perfusion in the visible portion of the nerve head. Hayreh has argued that the region behind the lamina cribrosa may be important in ischemic damage from high intraocular pressure [60]. The postlaminar section, and much of the lamina cribrosa, would not be accessible for LDF examination.

DISCUSSION

Despite the development of highly sophisticated techniques for measuring blood flow, it is still unclear whether increased intraocular pressure in glaucoma causes ischemic damage to the optic nerve. Table 1 compares studies which examine the effect of intraocular pressure on nerve perfusion.

Differences in methodology may explain much of the variation in the results of optic nerve perfusion studies. Each of the techniques has its own particular strengths and weaknesses. Invasive methods allow for continuous monitoring of blood flow, but the consequences of electrode insertion into the nerve head are unknown. The microsphere technique is noninvasive, but it can give inaccurate results because of an insufficient number of microspheres in areas of low volume of flow; axial streaming and arterial obstruction are additional problems with this method.

Iodoantipyrine has improved resolution over the microsphere technique and is accurate in areas of low flow; tracer diffusion is the primary difficulty in iodoantipyrine flow analysis. High spatial resolution is characteristic of deoxyglucose, but it is unclear if the equations developed for the technique in brain are applicable to the optic nerve. Finally, doppler flow analysis, while correlating positively with iodoantipyrine data, gives no information about the retrolaminar region of the optic nerve.

When the different blood flow studies are examined by method, less variation in perfusion data is obtained. Table 1 indicates that each of the three studies employing iodoantipyrine shows autoregulation of blood flow to the optic nerve. The microsphere method and invasive techniques give less consistent results.

Clinical evidence exists which supports either an ischemic or a mechanical etiology for glaucomatous nerve damage [21]. Data from Caprioli indicate both these mechanisms may be involved in the pathogenesis of glaucoma, depending on the degree of the intraocular pressure increase [61,62]. Caprioli compared the optic nerve heads of patients with high- and low-tension glaucomas. He found optic nerve damage in one subgroup was primarily related to high IOP while nerve damage occurred in the absence of increased IOP in another group of patients. In the final analysis, the different findings of optic nerve blood flow studies may reflect a variable effect that intraocular pressure has on perfusion.

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