EXTENDED REPORT

Non-invasive vascular impedance measures demonstrate ocular vasoconstriction during isometric exercise

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Aims: The calculation of impedance for a vascular network is a common method used in circulation studies. Impedance indices (the ratios of the harmonics of pressure to the harmonics of flow) provide the investigator with a measure of the opposition to blood flow in a pulsatile system and are a proven indicator for vasculopathy. Previous studies investigating the eye's opposition to blood flow have concentrated on simple measures of resistance (the ratio of mean pressure difference to mean flow) which are more appropriate to a steady state or non-pulsatile system. The purpose of this study is to demonstrate a new, non-invasive, method to determine the vascular impedance of the eye during the known physiologic stress of sustained isometric exercise.

Methods: Waveforms of ocular blood flow and carotid arterial blood pressure were measured non-invasively. Ocular blood flow waveforms were calculated using the Langham-Silver method by measuring the small fluctuations in intraocular pressure over time with a high fidelity pneumatonometer. Carotid arterial blood pressure waveforms were determined using a SphygmoCor electronic tonometer held over the common carotid artery of the neck. Both waveforms were recorded simultaneously in normal volunteers under two conditions: (1) a baseline resting state and (2) during sustained isometric exercise. The components of the two waveforms (the harmonics) were calculated using a Fast Fourier transform and expressed as a ratio in order to determine a set of impedance values for each condition. The first four impedance values were calculated.

Results: 12 volunteers (six male: six female) with a mean age of 27 years (range 22–32 years) were recruited to the study. In comparison to baseline resting conditions, mean carotid blood pressure and heart rate both increased significantly during exercise: baseline mean carotid blood pressure, 82.6 ± 8.2 mm Hg vs exercise mean carotid blood pressure, 93.8 ± 12.8 mm Hg ($p < 0.001$); baseline pulse rate, 64.6 ± 9.1 BP_m vs exercise pulse rate, 71.8 ± 9.7 BP_m ($p < 0.001$). Compared to resting conditions, the first and third impedance values demonstrated significant change during exercise: the first impedance value rose (83.9 ± 25.6 mm Hg-s/ μ l to 117.1 ± 40.9 mm Hg-s/ μ l, $p = 0.01$) and the third impedance value fell (487.9 ± 294.7 mm Hg-s/ μ l to 248.3 ± 206.8 mm Hg-s/ μ l, $p = 0.01$).

Conclusions: The present study demonstrates, for the first time, a practical non-invasive method of calculating an index of impedance moduli for the pulsatile quotient of blood flow to the eye. Furthermore, during controlled isometric exercise, the impedance moduli displayed changes consistent with that known for a vascular system during vasoconstriction. The calculation of impedance moduli for the eye therefore shows promise for future investigations into ocular conditions where vascular obstruction is an aetiological factor.

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Vascular dysfunction has been implicated in numerous forms of eye disease. In many of these conditions, for example ischaemic optic neuropathy, the role of circulatory disturbance to the eye is obvious but in many, such as primary open-angle glaucoma (POAG), the aetiological function is less well defined.^{1–2} A number of methods to investigate the eye's vascular function have been developed.³ The majority examine parameters that relate to flow at various levels of the ocular vascular circulation, for example: colour Doppler spectral ultrasonography records the centre maximum velocity of blood travelling through retrobulbar arteries;⁴ digital video fluorescein and indocyanine green angiography graphically display the retinal and choroidal vascular beds respectively;⁵ and laser Doppler flowmetry can, by being directed at the avascular fovea, measure blood flow of the underlying choriocapillaris.⁶

The heart provides the driving force for the body's circulation and the resultant disparity of the blood pressure between heart and periphery, coupled with the opposition to perfusion by the smaller arteries and arterioles, combine to produce the main haemodynamic properties seen at an end-organ. In addition to a measurement of ocular blood flow, it is important therefore to

measure local perfusion pressure in order gain more complete knowledge of the system's vascular status. Mean ocular perfusion pressure is defined as $OPP_m = OABP_m - IOP$, where $OABP_m$ is the mean ophthalmic artery blood pressure and IOP is the intraocular pressure, taken to be equivalent to the eye's venous pressure. Sayegh and Weigelin^{7–8} measured the ophthalmic artery pressure in a total of 254 normal volunteers using ophthalmodynamometry and, using these data, a relationship of $OABP_m = 0.84 \cdot BP_m$, (where BP_m is the mean blood pressure) can be calculated for subjects in the supine position.⁹ Robinson *et al*¹⁰ also used the Bailliant ophthalmodynamometer to verify their calculation of OPP during isometric exercise from brachial blood pressure measurements. They found a similar regression formula of $OABP_m = 0.87 \cdot BP_m$ for three seated subjects. Knowing the $OABP_m$, a measure of mean resistance can be derived for the eye from Hagan-Poiseuille's law: mean ocular vascular resistance = $OABP_m / \text{flow mea-}$

Abbreviations: BP_m, mean blood pressure; IOP, intraocular pressure; OABP_m, mean ophthalmic artery blood pressure; OPP_m, mean ocular perfusion pressure; POAG, primary open-angle glaucoma

sure.¹¹ There are two possible limitations to the above approach of gauging the systemic contribution to the eye's circulation. First, the use of a general conversion formula to calculate ophthalmic artery blood pressure from brachial artery measurements is of use in group studies but is less reliable on an individual basis. Second, the classic Hagan-Poiseuille's law for calculating mean vascular resistance is appropriate to a steady state system of flow, but not where the system is inconstant or pulsatile.¹² Intraocular blood flow is pulsatile down to the level of the choriocapillaris lobules and the retinal capillaries.^{13–14} The proportion of arterial blood flow to the eye that is pulsatile is dependent on how far down the arterial tree the measurement is taken. In the short and long posterior ciliary arteries, the pulsatile component of blood velocity has been estimated as 55% of the mean velocity.⁹ In the subfoveal choriocapillaris, Riva *et al.*⁶ using laser Doppler flowmetry, found the pulsatile proportion to be 23%.

McDonald¹⁵ first suggested that the term impedance should be used when considering dynamic pulsatile flow and pressure in arteries, and that the term resistance should be confined to the "static", or mean flow, terms. Impedance is a frequency dependent measurement and allows a comparison of the ratio of driving blood pressure to resultant blood flow to be made for each component (harmonic) of the two waveforms. Impedance has been commonly measured in cardiovascular studies where its use has explored various properties of the arterial system, for example: the effects of vasodilating medication, high blood pressure and aging.^{16–18} The purpose of this study therefore was to investigate a non-invasive method of measuring an index of ocular vascular impedance using blood pressure values local to the eye.

MATERIALS AND METHODS

12 volunteers (six male: six female) with a mean age of 27 years (range 22–32 yrs) were recruited to the study. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Human Sciences Ethical Committee of Aston University, Birmingham, United Kingdom. Each volunteer gave written consent following an explanation of the experimental protocol and before an ophthalmic examination to rule out ocular abnormalities. Volunteers were only included if they had a visual acuity of 20/30 or better, no history of eye disorders or surgery and normal ocular findings. All reported that they were free of cardiovascular disease and not on any medication.

Blood flow waveforms were determined using the technique of Silver *et al.*¹⁹ to calculate pulsatile ocular blood flow. This method uses a high fidelity pneumatonometer (the Ocular Blood Flow Analyzer; Paradigm Medical Ind., Utah, USA) to continuously measure the microfluctuations in IOP associated with the cardiac cycle. The shape of each IOP pulse is taken to represent the change in intraocular volume as the internal ocular vessels ebb and flow during one heart beat. In order to calculate a measure of ocular blood flow, it is necessary to first convert the IOP pulse to one of ocular volume change using a pressure-volume relationship and second to differentiate the pulse to give rate of volume change, or flow.^{20–22} Tonometry measurements are taken at a rate of 200/s for up to a 10 s maximum capture time. For this study, six intraocular pressure pulses were recorded continuously and the duration of measurement lasted approximately 4–9 s, depending on the subject's heart rate. All measurements were taken from the right eye. Before recording, the volunteer's cornea was anaesthetised with one drop of proxymetacaine hydrochloride 0.5% (Minims Proxymetacaine, Chauvin Pharmaceuticals Ltd, England). The six complete intraocular pressure pulses were downloaded to a personal computer and averaged. The mean

pulse wave was transformed into a corresponding relative blood flow waveform through the use of a pressure-volume algorithm for the human living eye and differentiation.^{21–23} This technique has been validated as recording the pulsatile component of intraocular, primarily choroidal, blood flow and has been shown to have good reproducibility.^{22–24–25} An example of a volunteer's relative ocular blood flow waveform is shown in fig 1. Simultaneous to the measurements of ocular blood flow, waveforms of carotid blood pressure were recorded using an electronic applanation tonometer (Sphygmocor Rx Pulse Wave Analysis system; PWV Medical Pty Ltd, Sydney, Australia). The tonometer probe was placed over the right carotid artery (carotis communis), medial to the sternocleidomastoid muscle, on the lower third of the neck. The Sphygmocor tonometer has been verified as accurately determining peripheral arterial pressure waveforms with high reproducibility.²⁶ The Sphygmocor software automatically calibrates the tonometer's measurements using baseline measurements of brachial blood pressure. Measurements of brachial blood pressure were taken using an automated sphygmomanometer (Cardiotsens; Meditech, Budapest, Hungary) that uses an oscillometric algorithm which has been verified in accordance with the British Hypertension Society protocol.²⁷ Brachial blood pressure measurements were recorded from the right arm of volunteers using an appropriately sized cuff. The Sphygmocor Rx software requires 10 seconds of uninterrupted carotid blood pressure recording in order to calculate a mean waveform. Only waveforms having a quality index of over 85%, as determined by the instrument's software, were accepted for the study. An example of a volunteer's carotid blood pressure profile is shown in fig 2. The averaged pressure and flow waveforms were downloaded to a PC for analysis and calculation of the impedance moduli. Prior to the study, the Coefficients of Reliability (CoR) were calculated for the first five harmonics of impedance moduli using pairs of repeated measurements among a group of normal subjects. The coefficient of reliability estimates the average correlation between all possible pairs of observations.²⁸ For repeated measurements, as in this study, the coefficient was calculated via a one-way ANOVA as

$$CR = \frac{(kSSb - SSst)}{(k-1)SSst}$$

Figure 1 (A) Ocular blood flow waveform of a volunteer during rest and (B) the same volunteer's ocular blood flow waveform during exercise.

Figure 2 (A) Carotid arterial blood pressure waveform of a volunteer during rest and (B) the same volunteer's ocular blood flow waveform during exercise.

where SSb and SS_t are the sums of squares between subjects and in total, respectively, and *k* is the number of measurements taken, which is two in this study. The coefficient of reliability also provides a measure of the percentage variance of disagreement between repeated measures by calculating $(1 - CR) \times 100\%$. That is, measurements are perfectly repeatable when the coefficient of reliability is 1 and the percentage variance is 0%. The coefficients of reliability were calculated using proprietary software with the confidence intervals set to 95% (SPSS v12.0.1; SPSS Inc, Illinois). Table 1 shows that only the first four impedance moduli reached clinically acceptable CoRs and for this reason only the first four impedance moduli were studied in this study. Each waveform was sampled at 16 equally spaced data points. A Fast Fourier Transform was used to calculate eight harmonics from these waveforms.²⁹ Eight harmonics were calculated, although only the first four were used, in order to avoid the possible introduction of aliasing errors.³⁰

All measurements were taken with the volunteer supine on a couch. Volunteers were allowed to adapt for 15 min, in order to allow cardiovascular function to stabilise, before measurements were taken. Measurements were recorded under two conditions: (1) at rest, and (2) after 3 min of lifting a 2.2 kg weight approximately 10 inches above the couch with their left arm. The two conditions were randomised in order to give six pairs of measurements where the resting condition occurred first and six pairs of measurements where the conditions were reversed. All data were presented as their arithmetic mean $\pm$ SD. Normality of the data was checked by verifying paired data did not fall outside two standard deviations of error from the mean for skew and kurtosis. Student's paired two tailed *t* test was used for statistical analysis. Given the multiple testing from the same data set, a Bonferroni correction was made to the *p* Value.

RESULTS

The experimental condition of isometric exercise produced a significant increase in systolic, diastolic, and mean carotid blood pressure: table 2. No significant increase in carotid pulse pressure was found. Fig 3 shows the first four impedance moduli for the two experimental conditions. Compared to resting conditions, the first and third impedance moduli demonstrated significant change during exercise: the first impedance modulus rose (83.9 ± 25.6 mm Hg-s/ μ l to 117.1 ± 40.9 mm Hg-s/ μ l, $p = 0.01$) and the third impedance modulus fell (487.9 ± 294.7 mm Hg-s/ μ l to 248.3 ± 206.8 mm Hg-s/ μ l, $p = 0.01$). The second and fourth impedance moduli were not significantly different between the two conditions.

DISCUSSION

To the authors' knowledge, the present study is the first to show that an index of impedance can be calculated for the eye from non-invasive measurements of ocular blood flow and arterial pressure waveforms local to the eye. Further, our data demonstrate changes in impedance values characteristic of ocular vasoconstriction during isometric exercise. This study shows that in normal patients, impedance values peak at approximately 3 Hz. The arterial system has been historically modelled as a Windkessel—a German term for the historic fire engine compression chamber consisting of a water pump leading to a distensible air-filled chamber which has a small conduit (fire hose) leading off it.³¹ The pump represents the heart, the air-filled chamber takes the place of the capacitance in the blood vessel walls and the fire hose, the resistance formed by the small arteries. In this Windkessel model, the impedance moduli reduce from relatively high values at low frequencies to lower values as the frequency increases. This pattern does not support the finding in this study of low impedance values initially with a peak at around 3 Hz. Similar to our results however are actual vascular impedance indices reported by researchers on various arterial systems around the body which demonstrate peaks and troughs in impedance moduli across the frequency range.^{32–33} These departures from the simple fall in impedance values, that the Windkessel model would predict, have been attributed to wave reflections from the smallest end-arterioles interfering with the main standing wave produced from the heart and the variability of vessel compliance.³⁴ The Windkessel model has now been superseded

Figure 3 The first four impedance moduli at rest and during exercise: Y error bars represent standard error of mean; *indicates a significant change ($p < 0.05$) between rest and exercise conditions.

Table 1 Repeatability (within-visit agreement) of the harmonic moduli of impedance

	1st harmonic	2nd harmonic	3rd harmonic	4th harmonic	5th harmonic
Coefficient of Reliability	0.91	0.80	0.75	0.63	0.35
Level of significance	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p = 0.12$

Table 2 Carotid blood pressure and pulse rate characteristics of the volunteers under the two experimental conditions

	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	Mean blood pressure (mm Hg)	Pulse pressure (mm Hg)	Pulse rate (beats per min)
Baseline	114.9±11.5	67.9±8.1	82.6±8.2	34.5±7.1	64.6±9.1
Exercise	128.9±14.8	78.6±10.4	93.8±12.8	35.6±8.3	71.6±9.6
p Value	<0.001	<0.001	<0.001	=0.640	<0.001

by more elaborate electrical models that can simulate these patterns of wave reflection and vessel distensibility.³⁵ The pattern of impedance values found in the present study may therefore represent a profile of vascular characteristics, such as the arteries' distensibility, between the carotid artery and the eye.

In this study, sustained isometric exercise resulted in elevated vascular impedance at low frequencies (0.5–1 Hz), and reduced vascular impedance in the 2.5–3.5 Hz frequency range. The physiological stress test of sustained isometric exercise produces known changes in cardiovascular function and the peripheral arterial beds.³⁶ In contrast to dynamic exercise, static exercise produces increased mean blood pressure due to a strong exercise pressor reflex stimulated by reduced perfusion on the metaboreceptors within the contracting muscle. In addition, unlike dynamic exercise, there is not usually a significant change in cardiac pulse pressure. This proved to be the case in the present study where diastolic and systolic carotid blood pressure values rose in parallel, producing a significant change in mean blood pressure without influencing the pulse pressure. This enabled the investigation of impedance moduli during a relatively controlled rise in mean blood pressure with minimal changes on the driving pulse pressure. The blood flow measurement used in our study measures pulsatile blood flow from the uveal, primarily choroidal, vascular beds of the eye.³⁷ The choroid of the eye is highly vascular and, although it is thought to demonstrate no local autoregulatory function to perfusion pressure, is highly innervated with sympathetic nerve endings.^{38–39} These sympathetic efferents are triggered when baroreceptors in the aortic and carotid sinuses detect rises in arterial blood pressure to produce choroidal vasoconstriction in order to buffer the increase in perfusion pressure and protect the eye.^{40–41} Vascular impedance studies looking at the effect of vasoconstriction on an arterial bed have found a relative increase in impedance moduli at the lowest frequencies (0.5–2.0 Hz) and a relative decrease in impedance moduli at the mid-frequencies (2.5–6.0 Hz).¹⁶ These changes reflecting the alteration of compliance characteristics of the arterial bed.³⁴ The changes in the impedance moduli found in the present study, an increase in the impedance values for the lowest frequency bin and a reduction at the mid-frequency bin, are therefore consistent with an arterial system during vasoconstriction.

The evidence in this study, of vasoconstriction in the ocular arterial beds during increased ocular perfusion pressure, is in agreement with a number of other researchers who have investigated this area. The human retinal circulation has been shown to autoregulate down to perfusion pressures of approximately 30 mm Hg using blue-field entoptic phenomenon and laser Doppler velocimetry.^{42–43} In contrast to measuring in the frequency domain (as in our study), Michelson *et al*⁴⁴ simultaneously measured real time blood flow velocities of the ophthalmic artery and iridal vasculature in addition to systemic blood pressure during physical exercise. The finding that both the ophthalmic artery and iridal vasculature increased opposition to flow during exercise, demonstrated protection to the eye against overperfusion at both the macro- and microcirculatory

levels. In the choroidal circulation, which is more appropriate to the present study, stability of flow over a limited range of perfusion pressure has also been demonstrated. Fuchsjäger-Mayrl *et al*⁴⁵ used squatting exercises in normal subjects to increase OPP and measured choroidal blood flow with laser Doppler flowmetry at the fovea. A modest rise in blood flow (approximately 20%) only occurred once OPP had increased by more than 65%. In a comprehensive study of ocular haemodynamics during isometric exercise, Kiss *et al*⁴⁶ measured choroidal laser Doppler flowmetry, Doppler sonography of the ophthalmic artery and fundus pulsations using a laser interferometric process. All three measures only demonstrated significant change once OPP had increased 70% above baseline, again providing evidence of a regulatory process protecting the eye. Interestingly, while blood flow measurements for laser Doppler flowmetry and Doppler sonography increased during exercise, fundus pulsations decreased. The authors attributed this finding to a shift from pulsatile to constant flow in the choroidal circulation. Whether the stability of flow in the choroidal circulation is true autoregulation, or a neurogenic response to arterial baroreceptors described above, is still an area of debate. Mechanical manipulation of OPP in animals has provided some evidence that regulatory choroidal blood flow is not solely neurogenic. Kiel and Shepherd⁴⁷ found that changing OPP by alternately varying either blood pressure or IOP provided evidence for a myogenic mechanism over a limited range of perfusion pressures. Similarly, Reiner *et al*⁴⁸ have shown a regulatory capacity for choroidal blood flow during acute changes in blood pressure through transient blood withdrawal in pigeons. The authors speculate that a mixed myogenic and neurogenic regulatory process, like that of the cerebral arterial system, may be available to the choroid to control blood flow.

A non-invasive technique to measure an impedance index of the eye may prove of clinical use in a number of ocular and systemic conditions of vascular aetiology. Glaucoma has long been suspected of having an element of vascular dysfunction as its cause. Stroke has been found to be a risk factor for ocular hypertensive patients converting to a diagnosis of POAG.⁴⁹ Large epidemiological studies have found the risk of POAG rises with increasing blood pressure.^{50–52} In addition, greater variability in diurnal systemic blood pressure has also been indicated in POAG, particularly the so-called normal tension glaucoma variant.^{53–54} Evans *et al*⁵⁵ analysed the ocular pressure pulse of POAG patients using Fourier analysis in a similar technique to the current study but without the use of blood pressure values to calculate impedance. Significant differences in the second to fourth harmonic ocular pulse moduli were found between glaucoma patients and normal subjects. This would appear to indicate that the current study's technique of measuring an impedance index of the eye applied to the field of glaucoma is warranted. A number of other conditions, where anomalous impedance values may be suspected, would also be of interest to investigate using the current study's technique. These conditions include carotid artery disease, ischaemic optic neuropathy and diabetic macular oedema.^{1–56–57}

It is important to note that the measure of impedance in this study is not strictly "vascular impedance" for a number of reasons. First, the measure of blood flow used in this study represents an amalgamation of all the pulsatile ocular components of an eye during a heart beat and not just the pure flow of a single artery of interest. Second, the two respective locations of blood flow and blood pressure measurement were disparate and our measurement of impedance can only be assumed if the pressure waveform is similar to that arriving at the eye. Indeed, the location of blood pressure waveform measurement was at the carotis communis, a point somewhat remote from the eye. The authors would argue however that the ocular arteries arise from the common trunk of the carotid and thus make it a more appropriate location for measurement than, for example, the brachial artery which relates to an entirely different vascular bed. Given that the purpose of the study was to attempt a non-invasive method of determining an impedance index, the carotid artery is the only practical artery available and is superior to that of other clinically available arteries, such as the radial. Future studies would benefit from comparing the ophthalmic artery pressure pulse derived from ophthalmodynamometry to that of the carotid artery using sphygmocardiography. A further limitation of the present study was the lack of a separate local ocular vascular measure to verify increased resistance occurred during physical exercise. Subfoveal laser Doppler flowmetry as used by Riva and co-workers would provide a possible choice in future validity studies.⁵⁸ It is important to note that the method of blood flow measurement used in the present study has two limitations. First, there is some evidence that the ocular pressure-volume relationship, upon which the conversion of IOP pulse to volume pulse requires, has been shown to vary with mean arterial blood pressure. Kiel⁵⁹ has shown in rabbits that the steepness of the ocular pressure-volume relationship is dependent on mean arterial blood pressure. Bayerle-Eder and co-workers⁶⁰ used the ratio of IOP pulse (derived by pneumatonometry) to fundus pulsation (derived by interferometry) as a surrogate marker for the pressure-volume relationship. The administration of nifedipine in normal subjects caused a fall in mean arterial blood pressure and a significant fall in the ratio of these pulse measures. Second, the methodology of Langham-Silver to derive pulsatile ocular blood flow from IOP microfluctuations assumes that venous outflow from the eye is steady and not pulsatile.²² There is some evidence from colour Doppler ultrasonography that venous outflow does contain a pulsatile element.⁶¹ Both these influences on the measure of ocular blood flow used in this study may limit its findings. Future studies in this area would benefit from using an alternative method of measuring ocular blood flow. Given the accuracy with which small retrobulbar arteries may now be imaged with colour Doppler ultrasonography, future studies may benefit in using these velocity profiles to improve on the precision of the impedance measurement.

In conclusion, the present study demonstrates a new, non-invasive method of calculating an index of impedance moduli for the pulsatile quotient of blood flow to the eye. Furthermore, during controlled isometric exercise, the impedance moduli displayed changes consistent with that known for a vascular system during vasoconstriction. The calculation of impedance moduli for the eye therefore shows promise for future investigations into ocular conditions where vascular obstruction is an aetiological factor.

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