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Optic-nerve-head blood-flow response to increase in arterial blood pressure in humans

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**OPTIC-NERVE-HEAD BLOOD-FLOW
RESPONSE TO INCREASE IN ARTERIAL
BLOOD PRESSURE IN HUMANS**

THESE
PRESENTEE POUR L'OBTENTION DU DOCTORAT EN
MEDECINE

DIPLOME D'ETAT

TIFFANY LACHARME
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qu'on signe à la mairie ?...

OPTIC-NERVE-HEAD BLOOD-FLOW RESPONSE TO INCREASE IN ARTERIAL BLOOD PRESSURE IN HUMANS

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ABSTRACT

Purpose. Autoregulation in ocular tissues ensures constant blood flow despite variations in ocular perfusion pressure and may be impaired in ocular diseases. The purpose of this study was to investigate the effect of increased blood pressure (BP) and ocular perfusion pressure (OPP) during isometric exercise on optic-nerve-head blood flow (ONH-BF).

Methods. In 21 healthy subjects, aged 18–40 years, BP was measured using a Nexfin™ pneumatic transcutaneous sensor and blood flow was measured using laser Doppler flowmetry (LDF). OPP was defined as $(0.74 \times \text{mean BP}) - \text{intraocular pressure}$. Handgripping consisted of static contraction of the finger flexors at 30% maximum contraction force using a hand dynamometer for 2 min.

Results. Data were analyzed in 15 healthy subjects, exhibiting a homogeneous response of BP to handgripping (linear regression of BP versus time). A large increase, up to 50%, in OPP during exercise was not associated with a proportional increase in ONH-BF; vascular resistance increased about 30%. The blood flow–pressure relationship showed blood flow significantly increased by approximately 30%, mainly due to the rise in velocity.

Conclusion. These new data strongly support the notion of autoregulation in ocular blood flow, protecting the eye from overperfusion. However, the increase in OPP is not completely counterbalanced despite the regular increase in vascular resistance. This blood flow regulation is possibly due to vasoconstriction, taking place outside of the sampled volume, probably in the arterioles proximal to the capillary bed of the neuroretinal rim. In the future,

real-time measurements of vascular resistance during handgripping could be investigated in glaucoma patients.

Key words. Laser Doppler flowmetry, optic nerve head blood flow, isometric exercise, autoregulation, vascular resistance

INTRODUCTION

Blood flow in the eye has been reported to exhibit autoregulation, which is the intrinsic ability of a tissue to maintain relatively constant blood flow (BF) despite variations in perfusion pressure. It is likely that the mechanisms underlying autoregulation rely on a balanced contribution of myogenic and metabolic components.^[1] In healthy subjects, autoregulation during an increase in ocular perfusion pressure (OPP) has been demonstrated for the choroid,^[2, 3, 4] the retina,^[5, 6] and the optic nerve^[7, 8] of the human and the animal eye.^[9-13] For instance, alteration of choroidal blood flow autoregulation has been reported in patients with various systemic diseases, such as those with vasospasm,^[14] diabetes,^[15] and a number of ocular diseases such as central serous chorioretinopathy,^[16] or after retinal detachment surgery.^[17] Abnormal autoregulation of the choroidal circulation has also been demonstrated in smokers.^[18] In contrast, there have been few studies in the human optic nerve head and the autoregulation process has not yet been precisely characterized. In all these studies, the arterial pressure was acutely increased by means of dynamic^[2, 19-21] or isometric exercise (handgripping^[14] or squatting).^[3, 4, 15-17, 22-24] (*Khayy and al., ARVO 5013 D861 2010, Choroidal blood flow response to isometric exercise in patients with obstructive sleep apnea syndrome.*)

Until now, arterial pressure has been measured by sphygmomanometry at discrete times. Therefore, the relationship between

change in BF and change in OPP (pressure–flow relationship) was determined using only a limited number of blood pressure (BP) values. The advent of new devices enabling the continuous measurement of arterial BP^[25] has now made it possible to investigate the autoregulatory capacity of optic-nerve-head blood flow (ONH-BF) more accurately.

The purpose of this study was to investigate, in healthy subjects, the time course of arterial blood pressure and ONH-BF, both measured simultaneously and continuously, for 2 min during isometric exercise and to characterize the response of the ONH-BF to increases in OPP.

MATERIALS AND METHODS

Study population

Included in the study were 21 healthy non-smoker subjects, aged 18–40 years. The exclusion criteria were local or general medication, ocular or systemic disease, pregnancy, infection, and reduced motility. The inclusion inspection comprised a full ophthalmological examination (visual acuity and refraction, slit lamp examination, intraocular pressure (IOP), funduscopy, and pachymetry), a general exam with supine and standing BP measurements, and an electrocardiogram.

The study was conducted in accordance with the Declaration of Helsinki for research involving human subjects and adhered to Good Clinical Practice guidelines. Informed consent was obtained from the subjects after explanation of the study. The study protocol was approved by the local institutional review board (IRB #6705) and was registered on ClinicalTrials.gov (NCT00874913).

Optic-nerve-head flow measurements

The laser Doppler flowmetry (LDF) instrument used in this study to measure optic-nerve-head blood flow (ONH-BF) has been described previously (M. Geiser *and al.* *EVER meeting 2008, e5315, New optical device for functional studies of the optic nerve head*). ONH-BF is obtained from the superficial layer of the optic nerve head. The instrument uses a coherent near-infrared probing beam (785 nm, 90 μ W at the cornea) that conforms to the American National Standards Institute (ANSI) standard

Z136.1 for laser safety. The beam is focused on the optic nerve head by asking the subject to look at a fixation target consisting of a point-like light. Light backscattered by the tissue in the sampled volume is collected by an optical system that directs the light to an avalanche photodiode. The output photocurrent is sampled at a frequency of 240 kHz with a 16-bit resolution and processed with Labview software to ascertain the ONH-BF parameters in real time at a rate of 17 Hz, using an algorithm based on photon diffusion and probabilistic theory. These parameters are: velocity, ONH-Vel (kHz); volume, ONH-Vol (in arbitrary units, a.u.); and relative flow, $ONH-BF = ONH-Vel \times ONH-Vol$ (a.u.), of the red blood cells within the sampled tissue region. The software automatically rejects signals for which the light intensity (DC, direct current) is not within $\pm 10\%$ of its most frequent value, for which the volume is suddenly too large (by at least a factor of three within 1/17 second), due to micro-saccades, for example, and for which the power spectrum is too close to the noise spectrum (value at Doppler shift frequencies around 0.5kHz should be at least three times larger than the noise evaluated around 15kHz). Two or more continuous 30-s recordings of the ONH-BF parameters were obtained for each measurement and a minimum of 12 s of valid measurement in each eye was further analyzed.

Study protocol

Patients were asked to abstain from alcohol and caffeine for at least 12 h before undergoing measurements. LDF was performed on the dominant eye, which was dilated with one drop of tropicamide (Théa, Clermont-Ferrand, France).

A monitor with a pneumatic transcutaneous sensor Nexfin™ (Bmeye, Amsterdam, The Netherlands) provided continuous systolic, diastolic, and mean blood pressure measurements.^[25]

The IOP of the fellow eye was measured using the Tono-Pen XL™ electronic tonometer (Oculab, Glendale, CA, USA)^[26] after the instillation of a contact anesthetic (oxybuprocaine, Novartis Pharma Rueil-Malmaison, France) during another similar experiment, in order to avoid interference with the LDF measurement. Three to six successive measurements were taken to reach the mean value, with variability less than 5%. Mean OPP was calculated with the following formula: $OPP_{\text{sitting position}} = (0.74 \times MAP) - IOP$,^[27] in which mean arterial pressure (MAP) was calculated as: $MAP = DBP + 1/3 (SBP - DBP)$. The vascular resistance was calculated as $R = OPP / \text{Flow}$.

Scheduled resting periods for each subject were at least 20 min in a sitting position before the study. Stable baseline conditions were established, ensured by repeated measurement of blood pressure. Handgripping consisted of static contraction of the finger flexors to 30% maximum contraction force using a hand dynamometer (Hydraulic Hand dynamometer, Model SH5001, Korea). During the 2 min of handgripping, continued measurements of ONH-BF were taken. If necessary, a second experiment could be performed, after a rest interval of 20 min.^[28]

Statistical analysis

Data are presented as mean \pm SEM (standard error of the mean) and median \pm 25% and 75% quartiles. Normality was assessed using the Shapiro-Wilk test. Normalized data during the experiment were calculated

according to baseline data. ONH-BF and resistance data were compared to the increase in OPP intervals within 5% increments (therefore 13 intervals were analyzed). A mixed model was used given the repetition of data over time and among the subjects. Given the non-normality of the data, the analysis was based on their ranks and their medians; for this reason, the results were presented as median \pm 25% and 75% quartiles. The p -value was assessed using Bonferroni correction (the corrected p -value for post hoc analysis was 0.0008). The data analysis was conducted with SAS 9.1 and linear regression was performed with Generalized Estimating Equations.

Sensitivity (the minimum statistically significant change in a given LDF parameter (S) that could be detected) was calculated using the formula:^[3]

$$S = (t * SD) / (\sqrt{n} * P_{mean}) * 100$$

where P_{mean} is the mean value of the LF parameter over all measurements, SD the standard deviation of the difference between the paired measurement for all subjects (two baseline measurements), and t the two-tailed value of the t distribution at a 0.05 significance level for the $n-1$ degree of freedom.

For the analysis of frequencies, after replacing the data points excluded from the software by linear extrapolation, a Fourier analysis was done using the freeware *R statistics*. The 120 seconds of the recording during the handgrip were cut into three 60 seconds length period (from 0 to 60sec, 60sec to 120sec and 30 to 90sec). The three resulting Fast Fourier Transforms (FFT) were average and displayed as a function of the period instead of the usual representation as a function of the frequency.

RESULTS

The data of 15 (eight males and seven females; mean age, 28 ± 2 years) out of 21 healthy subjects tested were analyzed. These subjects were good responders to handgripping, i.e., they had a homogeneous BP response to handgripping. A homogenous BP response was defined as having a BP time profile during the 2 min of handgripping exercise with an increase greater than 30% of baseline BP. These 15 subjects exhibited a mean increase in BP over time of $40 \pm 3\%$ and a positive correlation over time ($p < 0.0001$). For these 15 subjects, measurement sensitivity was 11.7% for ONH-BF, 12.7% for volume, and 4.2% for velocity (calculated with two continuous baseline measurements lasting 20 s). Measurements were taken at a temporal location head in 67% of the cases and at an inferior temporal location of the optic disk in 33%.

At the end of the exercise, the IOP was $13 \pm 4\%$ i.e., 1.3 ± 1 mmHg higher than at the baseline.

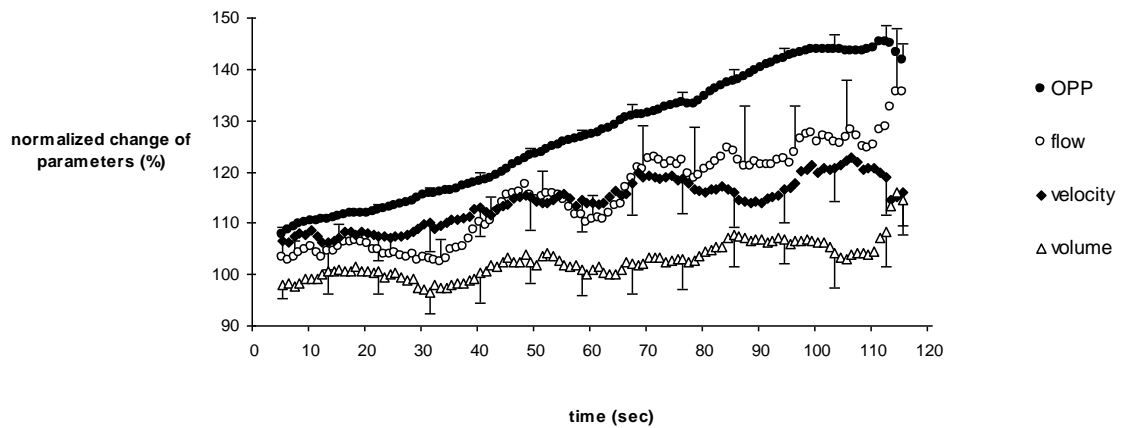


Figure 1: Optic nerve head blood flow velocity, volume, and mean arterial pressure over 2 min of handgripping in 15 healthy subjects (Data presented as mean of the moving average \pm SEM)

Figure 1 illustrates the MAP and ONH-BF response over 2 min of handgripping. Handgripping induced a continuous increase in MAP and OPP up to 138 ± 1 and $145 \pm 1\%$, respectively, at the end of the exercise (mean values based on the last ten raw data) ($p < 0.0001$). ONH-BF increased regularly during isometric exercise, as long as the handgripping persisted, in parallel to the increase in MAP and OPP, up to $131 \pm 3\%$. Regression of ONH-BF values versus time shows that ONH-BF increased progressively and significantly with time ($p < 0.0005$). The analysis of BF parameters across time suggested that the increase in flow was mainly associated with variations in velocity. Handgrip induced an increase in velocity and volume up to 117 ± 1 and $113 \pm 2\%$ (mean values based on the last ten raw data), respectively, at the end of the handgripping exercise.

Figure 2 shows the correlation between ONH-BF and increasing OPP intervals. Analysis showed a significant difference between the intervals ($p < 0.0001$). For a 50% increase in OPP, flow increased by only 15%. Regression of ONH-BF versus OPP values shows that flow increased significantly when OPP increased from 100 to 145% ($p = 0.0002$).

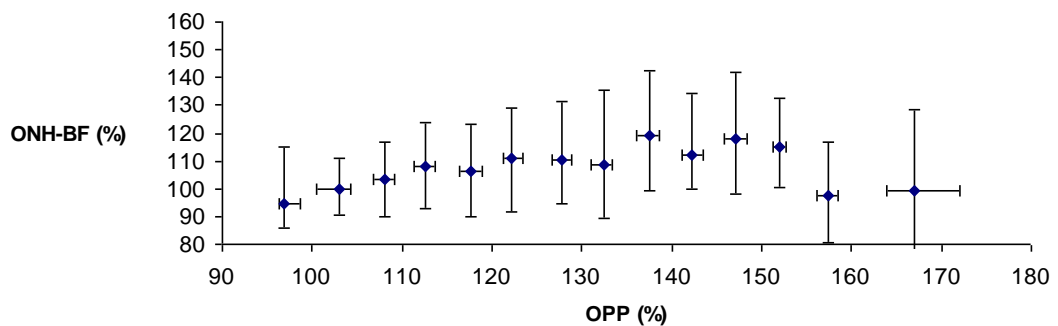


Figure 2: Change in ONH blood flow versus OPP in 15 healthy subjects over 2 min of handgripping. Each data point represents a median of successive flow values of the percentage change in OPP (data presented \pm 25 and 75% quartiles)

In all subjects, the increase in vascular resistance versus OPP during handgripping showed a significant linear relationship as a function of the OPP ($p = 0.0013$, Figure 3). For instance, a 50% increase in OPP was associated with a 30% increase in resistance. At the end of the exercise, the mean vascular resistance was increased by as much as $125 \pm 2\%$.

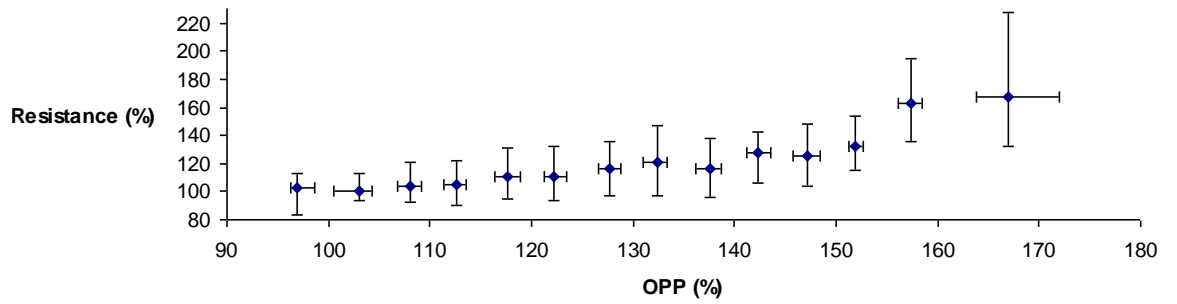


Figure 3: Change in resistance versus OPP in 15 healthy subjects over 2 min of handgripping. Each data point represents a median of successive resistance values of the percentage change in OPP. (data presented ± 25 and 75% quartiles)

We could roughly identify four particular response patterns of ONH-BF to increase in OPP in this experiment, as illustrates figures 4.

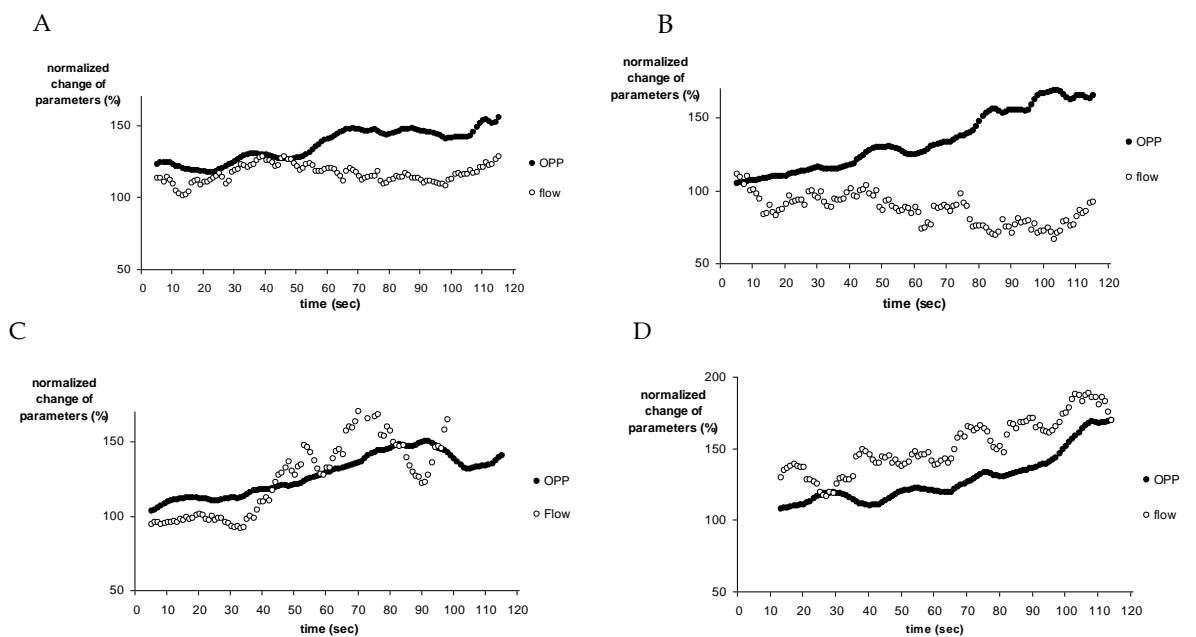


Figure 4: Examples of ONH blood flow and MAP in four subjects (#20, 1, 3,

and 12) during handgripping (Data presented as mean of the moving average)

In the first case (subject #20, figure 4A), handgripping induced a 155% increase in OPP, whereas ONH-BF remained relatively constant during the 2 min of exercise. For the second case (#1, figure 4B), in spite of a continual increase in OPP (165%), flow tended to decrease during handgripping to -8% from baseline at the end of the exercise. Subject #3 (figure 4C) showed a BF response with two distinct phases during OPP increases, a phase of stability in flow followed by increases in ONH-BF to 177% (C). Finally, subject #12 (figure 4D) showed an almost parallel increase in both parameters during handgripping; OPP and BF increased 170%, at the end of the exercise.

In some subjects, the analysis of blood flow parameters across time suggested oscillations in ONH parameters during the exercise (see example in Figure 5). Oscillation in ONH-BF with a period of approximately 15–20 s (frequency, 0.06–0.05 Hz), synchronized to volume fluctuations. In 75% of the subjects, a phase shift of approximately 180° between volume and velocity changes was found.

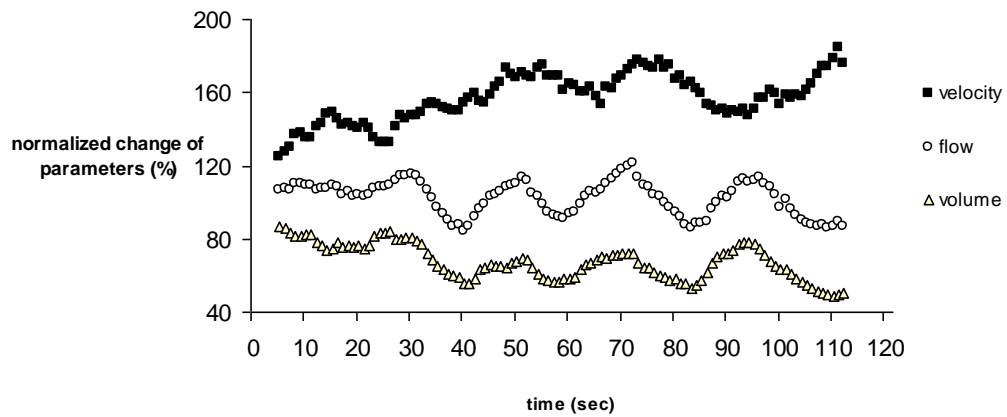


Figure 5: ONH blood flow, velocity, and volume in subject #5 during handgripping exercise (data presented as mean of the moving average)

Figure 6 shows the spectral Fourier analysis of velocity and ONH-BF in three of the subjects. Oscillations lasting 1 s and 3 s corresponding to frequencies of 60 cycles/min (1 Hz) and 20 cycles/min (0.3 Hz), respectively, predominated in this analysis. The lower frequencies shown in Figure 5 did not appear due to the short duration of the handgripping experiment (2 min).

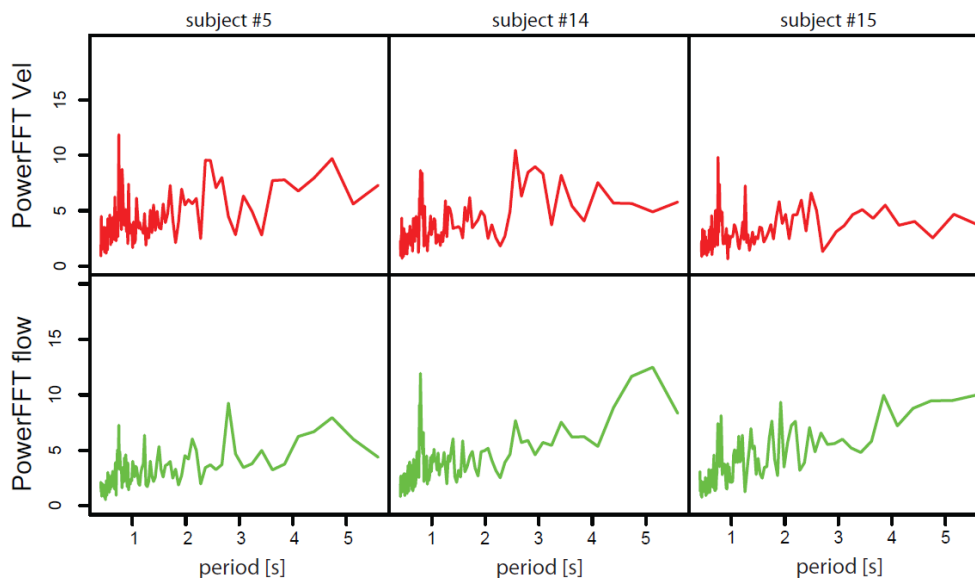


Figure 6: Power spectrum of the LDF recording for velocity and ONH-BF of three subjects

DISCUSSION

This experimental study in healthy humans provides new insight into the relationship between ONH-BF and BP, i.e., a constant increase in vascular resistance associated with the continuous increase in BP. These new data illustrating the autoregulation process of BF in the ONH suggest that the increase in vascular resistance does not fully counterbalance the increase in OPP over the 2 min of isometric exercise.

An increase in arterial pressure can be obtained after intravenous injection of drugs in humans and animals, such as adrenaline,^[29] norepinephrine, angiotensin II,^[30] kallikrein, bradykinin, and angiotensin I and II,^[31] or using occluders on the thoracic aorta and inferior vena cava in animals.^[32] A noninvasive alternative in humans is to increase BP during isometric^[4, 33] or dynamic exercise.^[34-36] Handgripping is an isometric exercise that causes a greater increase in BP than dynamic exercise^[34-36] principally by stimulating the sympathetic nervous system.^[37, 38] This is a reproducible and noninvasive test of sympathetic function with a well-defined reflex pathway,^[39] leading to an increase in muscle sympathetic nerve activity and plasma catecholamines. Isometric exercise also increases heart rate, arterial BP, cardiac output, left ventricular contractility, and systemic vascular resistance.^[28, 40-42] The cardiovascular effect depends mainly on the intensity of the isometric contraction and the duration of the isometric exercise,^[43] irrespective of muscle mass.^[44] In this experiment, we selected healthy subjects who obtained a regular and significant increase in BP in order to obtain a homogeneous group. The variability in the response can be due to a contraction that represents a very low percentage of the true maximal

voluntary strength.^[28] The approach used herein is also original since all previous studies examined the relationship between BP and blood flow in a discontinuous manner, with measurements every 30 s or every minute^[2-5, 20, 45] or before and at the end of exercise.^[6, 20, 27]

This experimental primary result showed that the vascular resistance increase was regular over time, parallel to the increase in OPP. The increase in vascular resistance reflects the possibility of autoregulation in the ONH. Strictly speaking, autoregulation of flow is the intrinsic ability of a tissue to maintain relatively constant blood flow despite variations in perfusion pressure, which can be demonstrated in the absence of neural and hormonal influences.^[46, 47] The mechanisms underlying autoregulation are based on a balanced contribution of myogenic and metabolic components involving the interaction of factors released by the vascular endothelium, for instance, including nitric oxide.^[48] In the optic nerve head, the effect of sympathetic activation can be excluded due to the absence of ortho- or parasympathetic innervation in humans.^[49, 50]

The existence of autoregulation at the ONH site was demonstrated in healthy subjects by Movaffaghy in 1998^[8] when OPP was increased during squatting, and in 1997 by Riva^[51], when OPP was decreased after a rapid rise in IOP. These results also suggested that the autoregulation mechanism was limited to 30–60% of OPP above baseline.^[22] In contrast with previous studies using discontinuous measurements, the continuous ONH-BF and BP measurements used in the present investigation allowed studying the dynamic autoregulation^[13] as previously described in nonhuman primates. The present results suggest constant blood flow-regulating kinetics (with regular increase in vascular resistance) allowing stability of blood flow for low

levels of BP increase and a limited autoregulation capacity with higher levels of BP increase. As suggested in Figures 3 and 4, some variability exists among healthy subjects with autoregulatory mechanisms leading to a stability of ONH-BF during increase in OPP in 10 out of 15 healthy subjects.

Whereas one previous study combining real-time measurement of BP and choroidal blood flow (ChBF) in healthy subjects during biking (dynamic exercise) showed stable ChBF during the increase in OPP, a close linear model of the change in vascular resistance versus OPP was demonstrated ($y = 1.025x - 7.478$, $r=0.96$).^[2] The first study reporting the use of LDF for ONH-BF measurement during isometric exercise^[8] also suggested a linear relationship between vascular resistance and OPP ($r=0.92$) in two healthy subjects: ONH-BF started to increase when the OPP increase was greater than 30%. However, the data reported herein strongly suggest that the range of regulation is progressively overtaken with time.

In healthy subjects, the ONH-BF increase was associated with a proportional increase in velocity. This suggests that vasoconstriction, parallel to the rise of BP, takes place outside of the sampled volume, probably in the arterioles proximal to the ONH capillary bed of the neuroretinal rim, supplied by retinal arterioles and sometimes the posterior ciliary artery for the surface nerve fiber layer, and the fine centripetal branches from the peripapillary choroid for the prelaminar region.^[52] Other blood flow modifications before the eye may also contribute to this regulation. Velocity in the ophthalmic artery has been shown to increase by approximately 30% during dynamic^[19] or isometric exercise.^[4] The parallel rise between the ophthalmic artery pressure and the brachial artery pressure indicates that regulation is

achieved in the central retinal artery or in the posterior ciliary arteries.^[5, 19]

Autoregulation observed in the ONH is close to that reported for retinal blood flow. Continuous recording of retinal blood flow has not been reported to date. In response to an acute increase in BP, retinal BF remains stable with an up to 141% increase in BP. Autoregulatory mechanisms of the retinal and ONH vasculature probably share certain metabolic and myogenic mechanisms. Retinal vasoconstriction during isometric exercise is modified by ET-A receptor blockade, indicating that endothelin-1 is involved in this process.^[53] On the other hand, high levels of circulating noradrenaline have little impact on retinal blood flow.^[54]

The pressure–flow relationship and the kinetics of vascular resistance described in this study should be evaluated in further experiments in order to study the mechanisms involved, using pharmacological interventions on nitric oxide (after administration of the nitric oxide synthase inhibitor LNAME) or the endothelin system (ET_A receptor antagonist inhibitor BQ-123).^[55] For instance, ET receptor blockade has been reported to blunt retinal vessel response during isometric exercise, suggesting that endothelin-1 is involved in retinal blood flow regulation when OPP increases.^[53]

The analysis of ONH-BF variations during exercise showed rhythmic changes in BF parameters during exercise, previously described in rest conditions in animals ^[56-59] and humans.^[60, 61] The recurrent pattern of variations at 1 Hz are synchronous with the heart rate and represent oscillatory changes of arteriolar diameter induced by pulsatile flow of the cardiac cycle. The 0.3-Hz frequency is synchronous with respiration. The slower oscillatory patterns (0.06 Hz) already described in the ONH^[60] in basal

conditions but also in exercise conditions^[62] may correspond to vasomotor frequency or α waves, representing intrinsic myogenic activity of the smooth muscle cells in resistance vessels. According to Stefanovska,^[63] this oscillation is associated with blood pressure regulation. The smooth muscle cells in the vessel walls continuously respond to changes in intravascular pressure, known as the myogenic response. At the cellular level, vasomotion is associated with oscillations in intracellular calcium concentrations and membrane potential.^[64]

As illustrated in Figure 5, the fluctuations in volume and velocity were out of phase by 180°, as previously described in the minipig^[56], possibly the result of a change in venule diameter, predominantly present at the surface of the optic nerve head.

In the present study, the amplitude variation of fluctuations during exercise as compared with baseline data remains to be determined. Our analysis was limited by the duration of baseline measurements, too short for a rhythmic analysis of low frequencies.

With regard to the new LDF device, this technique has a high temporal and spatial resolution (*M. Geiser and al. EVER meeting 2008, e5315, New optical device for functional studies of the optic nerve head*). However, current limitations are the measurement of BF in arbitrary units, the limited penetration of the laser beam estimated at 300 μm ^[65], and the need for good ocular fixation.

In conclusion, the combination of real-time measurement of ONH blood flow using LDF and BP during isometric exercise provides a

noninvasive method precisely defining the blood flow–pressure relationship. The approach in patients with optic nerve vascular disease, such as normal tension glaucoma^[7] or nonarteritic ischemic optic nerve neuropathy, could also give insight into possible impaired autoregulation. Applications in patients should take into account the current limitations of the LDF system, however, such as optical considerations (refractive errors of the eye), the variability in ONH-BF response, and the requirement of stable ocular fixation.

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THESE SOUTENUE PAR : Tiffany LACHARME

OPTIC-NERVE-HEAD BLOOD-FLOW RESPONSE TO INCREASE IN ARTERIAL PRESSURE IN HUMANS

The combination of isometric exercise (handgrip) and real-time measurement of optic-nerve-head blood-flow (ONH-BF) using Laser Doppler flowmetry (LDF) provide a non-invasive method to define precisely the blood flow-pressure relationship. This prospective study was carried out in 15 healthy subjects: arterial pressure was measured using a pneumatic transcutaneous sensor Nexfin™ and the blood flow was measured using LDF. Ocular pressure perfusion (OPP) was defined as $(0.74 \times \text{mean arterial pressure}) - \text{intraocular pressure}$. Handgripping consisted of static contraction of the finger flexors at 30% maximum contraction force, using a hand dynamometer during two minutes.

Our results showed that a large increase in OPP during exercise was not associated with a proportional increase in ONH-BF. These data strongly support the notion of autoregulation in ocular blood flow, protecting the eye from overperfusion. The blood flow-pressure relationship showed however that despite a certain increase of vascular resistance, blood flow significantly increased by approximately 30% (mainly due to the rise in velocity). These new data of the dynamic autoregulation process of blood flow in the ONH suggested that the increase in OPP is not completely counterbalanced despite the regular increase in vascular resistance in some subjects. This blood flow regulation is possibly due to vasoconstriction, taking place outside of the sampled volume, probably in the arterioles proximal to the

capillary bed of the neuroretinal rim. In the future, real-time measurements of vascular resistance during handgripping could be investigated in glaucoma patients who possibly have dysregulation of the ONH blood flow. Applications in patients should take into account the current limitations of the LDF system, however, such as optical considerations (refractive errors of the eye), the variability in ONH-BF response, and the requirement of stable ocular fixation.

Vu et permis d'imprimer

Grenoble, le 1^{er} Juin 2011

LE DOYEN

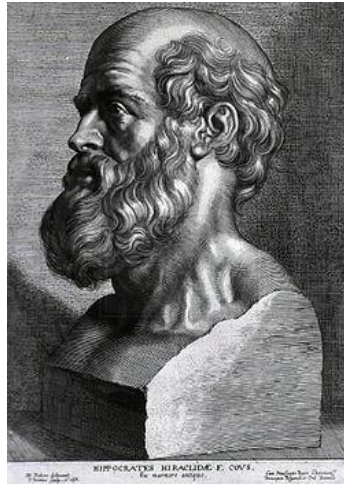


Pr ROMANET J. Paul

LE PRESIDENT DE THESE

A handwritten signature in black ink, appearing to be 'Pr Romanet J. Paul', is written in a cursive style.

Pr ROMANET J. Paul



SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciplines et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.