SUB-FOVEAL CHOROIDAL BLOOD FLOW BY LDF: MEASUREMENT AND APPLICATION TO THE PHYSIOLOGY AND PATHOLOGY OF THE CHOROIDAL CIRCULATION

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ABSTRACT

Laser Doppler flowmetry allows the measurement of relative choroidal blood flow in the sub-foveal region of the fundus (ChBF). This technique has been applied to the investigation of the regulation of ChBF in response to a variety of physiological stimuli (breathing different gas mixtures of O_2 and CO_2, varying the systemic and ocular blood perfusion pressures, light-dark transition and zero gravity) in normal subjects. Measurements in pathological conditions, such as diabetes, age-related macular degeneration and glaucoma indicate alterations of the response of ChBF to increased systemic blood pressure. The data provide a better understanding of the regulation of the choroidal circulation in the normal and diseased eye.

KEYWORDS

Sub-foveal choroidal blood flow, laser Doppler flowmetry, physiological stimulation, isometrics, hyperoxia, hypercapnia, diabetes, AMD

RÉSUMÉ

La fluxmétrie par laser Doppler permet la mesure du débit sanguin choroïdien (ChBF) dans la région sub-fovéolaire du fond de l'oeil. Cette technique a été appliquée chez l'homme dans le but d'investiguer la régulation de ChBF en réponse à une variété de stimuli physiologiques (inspiration de gaz contenant des mélanges différents de O_2 et de CO_2, variation de la pression systémique et de la pression de perfusion oculaire, transitions de lumière/obscurité, pesanteur zéro). La mesure de ChBF dans des conditions pathologiques telles que le diabète, la dégénérescence liée à l'âge et le glaucome démontre des altérations de la régulation lors de l'augmentation de la pression systémique. L'application de la fluxmétrie par laser Doppler permet d'obtenir une meilleure compréhension de la pathophysiologie de régulation de la circulation choroïdienne chez l'homme.

MOTS-CLÉS

Flux sanguin choroïdien sub-fovéolaire, flumétrie par laser Doppler, stimulation physiologique, exercices isométriques, hyperoxie, hypercapnie, diabète, DMLA

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INTRODUCTION

In the foveal avascular zone (FAZ), the retinal metabolism relies entirely on the supply of nutrients and oxygen from the choroidal circulation. Legitimately, one can assume that inadequate blood perfusion in the sub-foveal choriocapillaris, the innermost layer of the choroid, leads to some impairment of central visual function. The observation that the photoreceptors need virtually all the oxygen that the normal choroidal circulation can provide [23] lends support to this hypothesis. Along this line of thought, it has been hypothesized that age-related macular degeneration is a manifestation of a vascular problem resulting from an increased resistance to blood flow in the choroid underlying the FAZ.[11]

The widely recognized importance of understanding the pathophysiology of diseases such as glaucoma, diabetic retinopathy, age-related macular degeneration and others, has recently led to the development of new techniques for the non-invasive measurement of retinal blood flow and its response to various physiological stimuli.[19] These techniques have extended markedly our understanding of the vascular physiology of the retina and optic nerve in humans and of the vascular factors implicated in the pathogenesis of various sight-threatening ocular diseases. For the choroidal circulation, however, a parallel body of knowledge is still lacking due to the absence of valid techniques for reliably quantifying choroidal hemodynamics.

The feasibility of near-infrared (811 nm) laser Doppler flowmetry (LDF) to quantify the sub-foveal choroidal blood flow (ChBF) response to physiological stimuli has opened new avenues in the investigation of the physiology of the choroidal circulatory system. Various LDF flowmeters have been described to perform ChBF measurements. In the first published choroidal LDF flowmeter, the laser delivery and detection systems were adapted to a conventional fundus camera.[39] Studies were also performed using a LDF system mounted on a scanning laser ophthalmoscope.[35] More recently, a compact device was described that applies the optical principle of confocality for the delivery of the laser light to the site of measurement and the detection of the scattered light (Fig. 1 A).[15] With this new system, the light scattered by the red blood cells is collected by a bundle of 6 optical fibers and guided to an avalanche photodiode. Each fiber has a core diameter of 110 mm. They are arranged on a circle with a diameter of 180 μm, which is imaged around the incident beam at the fovea (Fig. 1 B). This detection mode represents the indirect mode of the confocal arrangement.

For the measurements of ChBF the subjects under test are asked to look directly at the laser beam, which appears as a faint pinpoint of red light. The signal from the photodiode is sampled at a rate of 21 times per second. The sampled values are Fourier transformed in a range of frequencies from 0 to 10 kHz to obtain the Doppler shift power spectrum.[16] From this spectrum, the following sub-foveal choroidal blood flow parameters are calculated:[42] ChB = mean red blood cell velocity, expressed in Hz; ChB = blood volume and ChBF = flux of red blood cells in arbitrary units. If the hematocrit remains constant during an experiment, ChBF is directly proportional to whole blood flow.

It is important to recognize that LDF technique provides only relative measurements of the flow parameters. The reasons are as follows.[42] Laser radiation upon a tissue undergoes scattering, as well as absorption by the tissue and the red blood cells. Both processes influence the penetration pattern of the laser light, which may differ from one region of a tissue to another, depending upon the spatial optical properties of the tissue. Thus, different tissue structures, as well as variations in this structure due to pathologies (for instance macular neo-vascularization) will affect the sub-foveal choroidal blood flow measurements.

The sensitivity of the sub-foveal blood flow parameters, e.g. the minimum change that can be detected in a group of subjects, has been determined for the confocal LDF device. Based on two 10-s measurements of the flow parameters performed at an interval of 30 min in a group of 21 normal volunteers, the averaged of the sensitivities between the two eyes for ChBVel, ChBVol, and ChBF were 4.9, 9, and 11.4%, respectively.[14]

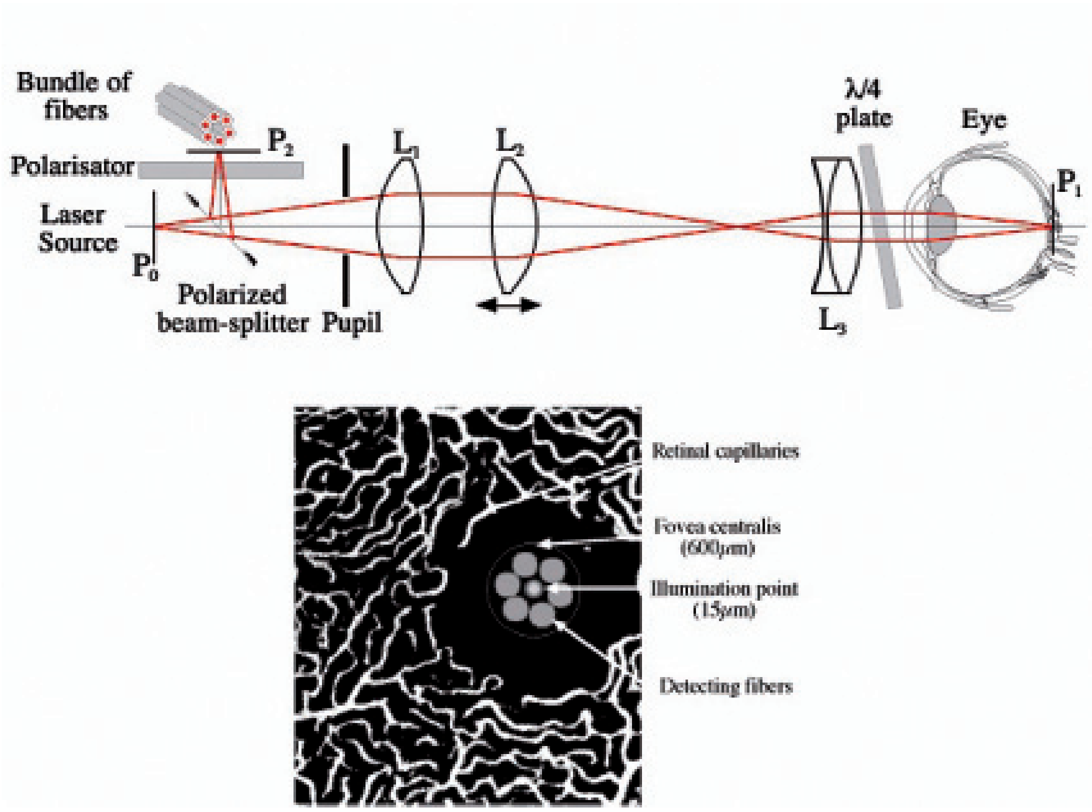

Fig. 1. (Top) Schematic representation of the optics of the confocal sub-foveal choroidal flowmeter. Pinhole P_0 is focused at P_1 in the plane of the retina by adjustment of lens L_2. The scattered light from the sub-foveal choroid is detected behind P_2. (Bottom) Cast of monkey region of the retina to illustrate the site of laser illumination and the optical fibers detecting the scattered light in the avascular zone. Numbers in parenthesis indicate approximate diameters. Reproduced from Geiser, Dierman and Riva [14] by permission.

APPLICATIONS TO THE PHYSIOLOGY OF SUBFOVEAL CHOROIDAL BLOOD FLOW REGULATION

The LDF technique described above is particularly suitable for investigating the regulation of ChBF in response to a variety of physiological stimuli. These stimuli include acute changes in the partial pressure of O_2 and/or CO_2 in the inspired gas, acute changes in the mean ocular perfusion pressure (PP_m = mean ophthalmic artery blood pressure - intraocular pressure) and light-dark transitions.

Changes in inspired blood gases

Investigation of the effects of various mixtures of O_2 and CO_2 (hyperoxia-hypercapnia) on ChBF demonstrates that ChBF is largely unaffected by changes in pO_2 but is strongly dependent on the pCO_2, when CO_2 is mixed with nearly pure O_2 (hyperoxia-hypercapnia).[15,39] The dose response curve of ChBF as a function of the pCO_2 is almost linear and the increase of ChBF is approximately 1.5 % per 1 mmHg increase in pCO_2, approximately 1/2 of the increase of cerebral and retinal blood flow.[15] Of particular interest is the effect of carbogen breathing (5 % CO_2 and 95 %

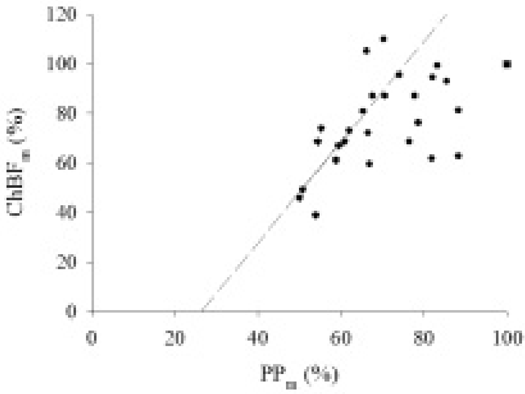

Fig. 2. Average (n = 14 eyes) sub-foveal choroidal blood flow ($ChBF_m$) change versus PP_{norm} when PP_{norm} is decreased by slowly increasing stepwise the IOP with suction cup. At each step, the suction was maintained constant for 2 min. Values of $ChBF_m$, the mean value of ChBF over the heart cycle, and PP_{norm} were normalized to 100 % (▪) at baseline. The regression line was based on $ChBF_m$ data with PP_{norm} below 65 %. Reproduced from Riva et al.[40] by permission of Lippincott-Raven Publishers.

O_2) since this gas mixture is assumed to prevent oxygen-induced vasoconstriction and therefore maintain or even increase blood flow while providing the retina with increased O_2 supply.[31] While in healthy male non-smokers carbogen breathing increases ChBF by 8 %, this procedure produces no significant effect in smokers.[49]

Changes in ocular perfusion pressure

Decrease of the mean perfusion pressure: The response of ChBF to decreases in PP_m induced by increases in intraocular pressure (IOP) is shown in Fig. 2.[40] The data demonstrate that the relationship between ChBF and PP_m is not linear. At high PP_m (IOP between 5 and 27 mmHg), ChBF remains mostly independent from PP_m. Beyond an IOP of 27 mmHg, ChBF decreases linearly with further decreases in PP_m and reaches a value of zero at a PP_m that corresponds to an IOP equal to the average systolic ophthalmic artery blood pressure.

These findings are similar to those obtained in rabbits when the perfusion pressure is decreased at constant systemic pressure.[21] They also suggest that the linear relationship used to fit choroidal blood flow versus PP_m measurements in cats and monkeys[1,3] represents only a first approximation to the actual relationship.

Increase of the mean perfusion pressure: PP_m can be acutely increased by having subjects perform various types of physiological manoeuvers. Three of these manoeuvers have been applied: static exercises in the form of isometrics, dynamic exercise achieved with biking, and body posture change.

Isometric exercise increases heart rate, arterial pressure and sympathetic nerve activity.[22] The effect of this maneuver on the sub-foveal choroidal blood flow is shown in figures 3 A and B.[41] The plot in figure 3 A represents the mean time course of ChBF during squatting and recovery from this exercise. During squatting PP_m increases by as much as 67 % but ChBF increased by only 12 %. ChBF plotted versus PP_m (Fig. 3 B) reveals that in normal subjects ChBF is largely independent from PP_m up to a value of PP_m of approximately 60 % above baseline. Similar findings were reported by others who also demonstrated that healthy male chronic smokers have an altered ChBF regulation.[48]

During isometric exercise, the blood pressure in the ophthalmic artery rises in parallel with that in the brachial artery and the IOP does not change significantly.[43] Therefore, the maintenance of ChBF close to the resting value in spite of the increase of PP_m must be achieved through an

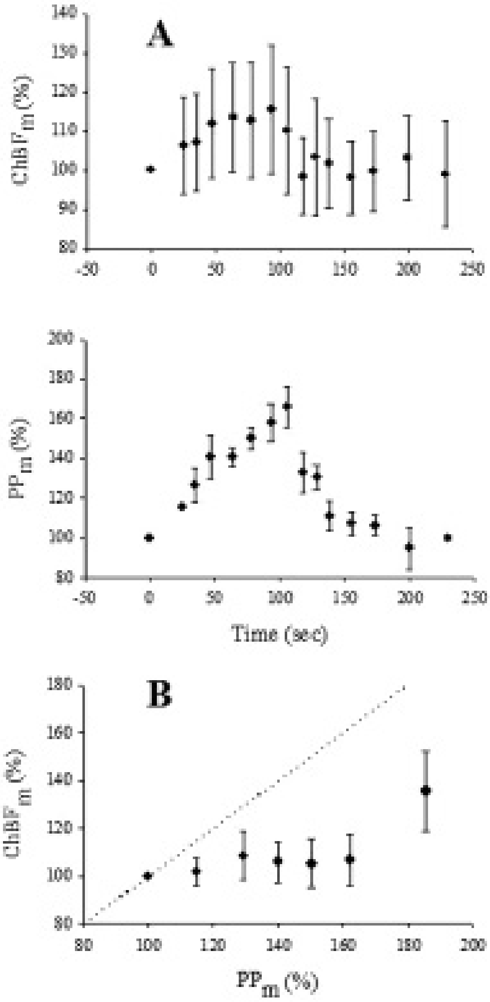

Fig. 3. (A) Time course of group average (n = 22 eyes, 11 subjects) of PP_m and $ChBF_m$ (the mean of ChBF over the heart cycle) during squatting and recovery from it. (B) $ChBF_m$ versus PP_m during squatting. Dotted line: $ChBF_m$ versus PP_m with no regulation (constant vascular resistance). Error bars: 95 % confidence limits of the mean. Adapted from Riva et al.[41] by permission of Lippincott-Raven Publishers.

increase in choroidal vascular resistance.[41] The protective role of ocular sympathetic vasomotor nerves in acute arterial hypertension has been demonstrated in cats and monkeys.[1-2,10] Figure 3 B indicates the presence of a similar mechanism in humans.

The effect of dynamic exercise, such as biking, on PP_m is shown in figure 4.[26] In spite of the rapid increase in PP_m during biking, ChBF remains very close (increase of about 6 %) to its value at rest (time 0 s). This study strongly supports the presence of an active regulatory mechanism for blood flow in the human choroid. Furthermore the study concluded that the increase in vascular resistance during biking is at the level of the choriocapillaris but the nature of the mechanism underlying this regulation remains to be elucidated.

Body inversion represents a simple and convenient method to change the ocular perfusion pressure. For that reason, it has been widely used as a provocation test for this circulation. Several studies have described the effect of body posture on the optic nerve and retinal circulations.[6-7,19,47]

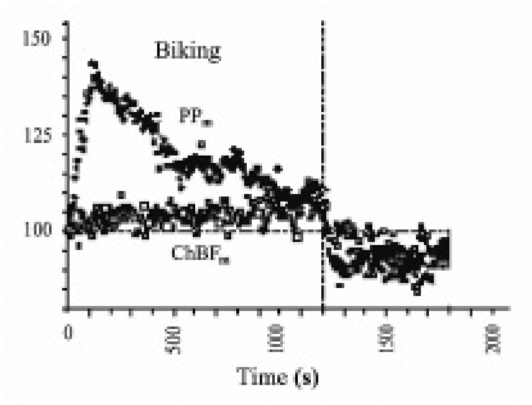

Fig. 4. Normalized group averaged (n = 14) $ChBF_m$ (averaged over the heart cycle) and PP_m as a function of time during 20 min of biking at a heart rate of 140 bpm. Although the biking causes the PP_m to increase up to 43 %, ChBF does not increase by more than 10 % above resting value. Adapted from Lovasik et al.[26] by permission of the Association for Research in Vision and Ophthalmology.

For the choroidal circulation, studies have been limited to the assessment of the effect of posture change on the pulsatile component of choroidal blood flow.[20,46] Recently, a study was conducted with the aim to assess the effect of posture change on the non-pulsatile and mean components of sub-foveal choroidal blood flow.[25] ChBF was measured continuously as the subjects tilted from upright (90°) to supine (-8°) positions and back to upright. Changing body posture from upright to supine increases mean ChBF by an average of 11 %. This increase is mainly due to a statistically significant 8 % change in mean ChBVel. This increase is mainly due to the increase of the non-pulsatile component.[25]
The expected PP_m in both the upright and supine positions has been assessed by Bill[7] from hydrostatic considerations. When Longo et al.[25] applied this analysis to their data they obtained a PP_m of 57 mmHg in the standing position and 70 mmHg in the supine, which represents an increase of ~ 23 %. If Bill's model were representative of the events occurring in the body, one would have to conclude that an active mechanism is operating to keep ChBF in supine posture close to its value in upright position. Experimental data obtained by ophthalmodynamometry in healthy volunteers under upright and supine conditions [45] lead, however, to a different conclusion. Indeed, based on these data, Longo et al.[25] found that PP_m increases by only 11.6 % between upright and supine postures. This percentage change, which is nearly equal to the change observed in ChBF, corresponds to a passive response of the choroidal vasculature to the increase in PP_m. It also suggests the presence of a compensatory mechanism that is already acting between the heart and the eye to buffer most of the increase in the blood pressure induced by the tilting from upright to supine. This mechanism could operate in the ophthalmic artery or already at the level of the internal and common carotid arteries.[44]

Zero gravity

Conditions of reduced gravity environment induce changes in blood pressure, IOP and sympathetic muscle activity, as well as shifts of body fluids to the upper extremities. Moreover astronauts often experience a decrease in visual acuity during orbital flights.[4] The etiology of this visual acuity change is unknown. To investigate the potential role of the choroidal circulation in this phenomenon, a miniature head-mounted laser Doppler flowmeter has been designed [16] and tested in normal volunteers in flights with parabolic trajectories. Preliminary data suggest that in zero gravity environment there is a consistent pattern of elevated ChBF (approximately 75 %) in the presence of lower diastolic and systolic blood pressure when compared to baseline values.[4]

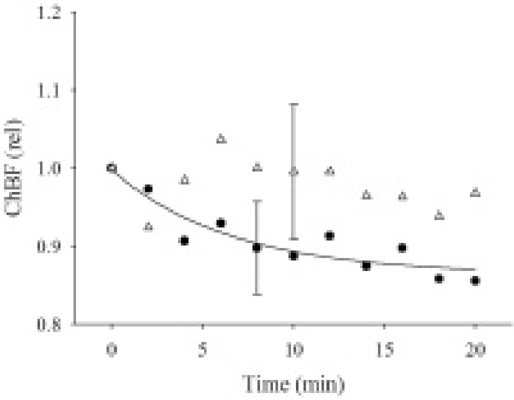

Fig. 5. Time course of the group means (n = 8 eyes) of ChBF during 20 min at room light (Δ) and during darkness (●). No significant change occurs at room light. A log regression (continuous line) reveals significant decreases in ChBF during darkness. Error bars are ± 1 SD. Adapted from Longo, Geiser and Riva[24] by permission of the Association for Research in Vision and Ophthalmology.

Light-dark exposure

One of the physiological functions of the high-flow choroidal circulation is the maintenance of a stable temperature environment for the outer retinal layers. This is particularly the case for the macular region.[8] This function is achieved, presumably, through both passive and active mechanisms, the latter involving a reflexive increase in choroidal blood flow in response to light.[34] The precise neural circuitry mediating this light-induced increase in choroidal blood flow is unknown. A number of theoretical investigations, however, have concluded that cooling of the retina during strong laser light exposure can occur without active increase in choroidal blood flow.[9, 27, 47]

In humans, the evidence that choroidal blood flow can be modulated by light has been obtained based on measurements of the temperature of the conjunctiva during light exposure of the contralateral eye.[32-33] Measurements performed in the measured eye in mammals (rabbits) have failed to detect a response of choroidal blood flow to changes in light exposure.[28] These apparently controversial data have led to a study of the response of ChBF, which did not confirm the presence of an active process of ChBF regulation in response to light exposure in the measured eye.[24] This study demonstrated, however, a reversible decrease in ChBF occurring after a transition from room light to darkness. The time course of this decrease is shown in figure 5. It was mainly due to a decrease of ChBVel. Further investigations of this response confirmed these findings and, in addition, showed that ChBF decreases in both eyes during a unilateral light-dark transition. This data support the hypothesis that a neural control mechanism underlies the adaptation of blood flow to the retinal illumination.[12,24] The fact that neither propranolol nor atropine have an effect on the ChBF response warrant further studies of the putative mechanism underlying the behavior of the sub-foveal choroidal circulation.[13]

APPLICATIONS TO THE PHYSIOPATHOLOGY OF SUB-FOVEAL CHOROIDAL BLOOD FLOW REGULATION

Diabetic retinopathy

Histological studies have demonstrated both early and late choroidal vascular lesions during the development of diabetes. Among the potential etiological factors of these lesions are hyperglycemia, alterations of the vessel endothelium and/or alterations of blood flow and its control. The effect of these factors on choroidal blood flow is still unclear. Alterations over the long term of the autonomous nervous system could lead to pathological changes of the mechanism regulating ChBF. This hypothesis was tested in Type I diabetics by assessing the ChBF response to increases in blood pressure induced by isometric exercise (squatting).[30] While in patients without diabetic retinopathy (NDR) ChBF responded normally to the increase in PP_m, i.e. ChBF remained largely unaffected by the increase in pressure, it increased linearly in the patients with retinopathy (DR). The DR patients also had an altered pupillary reflex. These data confirm an alteration of ChBF regulation in DR is at the level of the autonomous nervous system.

Other ocular diseases

Alterations of the regulation of choroidal blood flow in response to increases in perfusion pressure induced by static exercise (isometrics or hand-grip) have been found in patients with pseudophakic eyes after encircling buckle procedure,[29] in patients with age-related macular degeneration,[38] patients with central serous chorioretinopathy[37] and patients with glaucoma.[17]
In conclusion, LDF measurements of the response of ChBF to various physiological stimuli have increased the understanding of the physiology of the choroidal circulation. The data obtained in a variety of ocular pathologies have demonstrated alteration of the regulation of sub-foveal choroidal blood flow in these pathologies and contributed to a better understanding of the disease process.

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