Literature Review

https://doi.org/10.31288/oftalmolzh202346773

Assessing quantitatively the state of the blood-aqueous barrier by laser flare photometry: a review

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This review discusses the experience in applying laser flare photometry, a non-invasive technique, in ophthalmology, to assess quantitatively the state of the blood-aqueous barrier (BAB) in patients with certain ocular and systemic disorders. The method allows reliable detection of such biomarkers of the state of the BAB as the intensity of the scattered light (flare) and number of cells in the aqueous of the anterior chamber, sometimes even at the subclinical level, which significantly improves the capability for early diagnosis and objective treatment monitoring.

Keywords:

laser flare photometry, blood-aqueous barrier, blood–ocular barrier, uveitis

The blood-aqueous barrier (BAB) consists of the non-pigmented ciliary epithelium, the posterior iridal epithelium, the endothelium of the iridal vessels, and Schlemm's canal endothelium, and is considered a part of the blood-ocular barrier (BOB). BAB breakdown due to ocular inflammatory response results in the appearance of intraocular inflammatory markers (cells and proteins) in the anterior chamber aqueous humor. The degree of BAB dysfunction depends on the severity of inflammation in the anterior segment of the eye. The more severe inflammation, the more proteins and blood cells are contained in the aqueous humor [1]. Inflammatory markers are commonly assessed clinically by slit-lamp biomicroscopy. Numbers of cells or cell aggregates in the aqueous humor are calculated [2], and proteins levels in the anterior chamber aqueous humor are determined based on the scattering of light by protein molecules (the Tyndall effect) [3].

The most well-known semi-quantitative slit-lamp biomicroscopy-based grading system for aqueous flare and aqueous cells was proposed by Hogan and colleagues as early as 1959 [4]. The system was subsequently modified by the Standardization of Uveitis Nomenclature (SUN) Working Group [3] (Table 1). A drawback of the latter grading system for intraocular inflammation is the dependence on the expertise of the observer that interprets the results of biomicroscopy.

In 1988, Sawa and colleagues developed a new objective, accurate and non-invasive technology, laser flare/cell photometry, to quantify flare and cells in the anterior chamber (aqueous humor), on the basis of the same principle that is applied in slit-lamp biomicroscopy [5]. The intensity of light scattering is proportional to the concentration of protein in the anterior chamber aqueous humor [6]. Laser flare photometry (LFP) is based on the same principle as slit-lamp flare evaluation, measuring back-scattered light from protein particles in the anterior chamber [7]. This instrument comprises of a constant power helium-neon or diode-power beam, which is directed at the target in the anterior chamber (Fig. 1). The backscattered light from the incoming laser beam is then detected and used for measurement. Scattered light from the anterior chamber goes through an optical focusing system and comes to a photoreceiver where it undergoes a photo-electro conversion process. Then, the collected data is analyzed at the analyzer unit to determine the intensity of light scattered by protein molecules in the anterior chamber aqueous humor (a flare value). Results are shown in the display. Laser flare photometry values are expressed as photon units per millisecond (ph/ms).

Laser photometry is a more objective technique for assessing the intensity of light scattered by protein molecules in the anterior chamber aqueous humor than slit-lamp biomicroscopy, since, in the former method, (a) the light source is a laser beam; (b) the detector is a photodetector/ photomultiplier and (c) the data is analyzed by a computer [8].

Instruments have been also developed for assessing the number of inflammatory cells in a particular volume of anterior chamber aqueous humor. Determining the number

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Table 1. Grading protein content (flare) and cell numbers in the anterior chamber

Protein content in the anterior chamber		Number of cells in the anterior chamber	
Grade	**Light scattering in the anterior chamber aqueous humor (aqueous flare)**	**Grade**	**Number of cells in the anterior chamber aqueous humor**
0	Absence of any notable flare	0	<1
		0.5+	1–5
1+	Faint flare	1+	6–15
2+	Moderate flare (iris and lens details clear)	2+	1625
3+	Marked flare (iris and lens details are hazy)	3+	26–50
4+	Intense flare (fibrin in the aqueous humor)	4+	>50

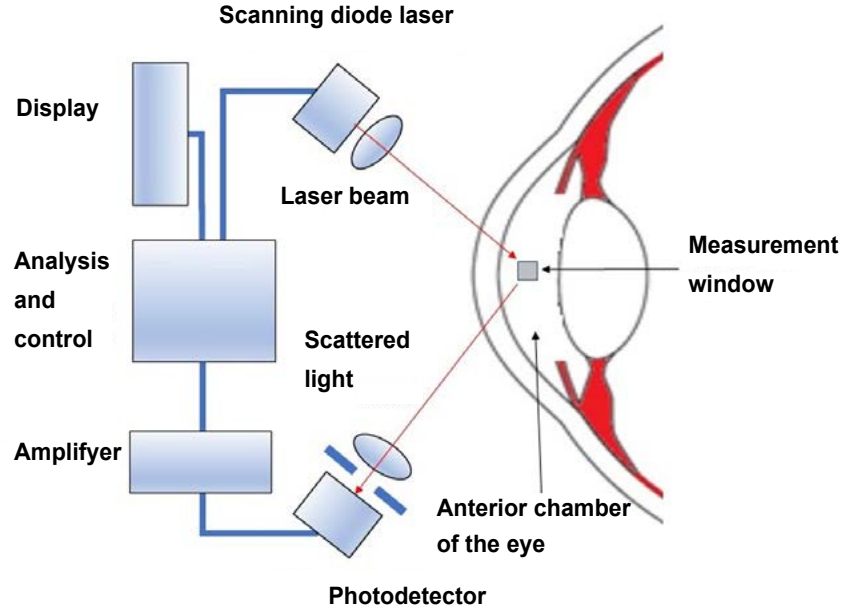

Fig. 1. Schematic diagram for laser-flare photometer recording of the intensity of light scattered by protein in the anterior chamber. The optical system of a laser flare photometer consists of a diode laser and photodetector arranged perpendicularly to the axis of the laser beam

of cells in the aqueous by laser photometry is based on the same principle of optically registering scattered photons from a laser beam directed into the anterior chamber. Whenever a peak in a particle exceeds 4 photon counts/400 μs, it is considered a cell and the total number of peaks counted by the computers gives the number of cells in the fixed measured volume [1].

At present, there are some limitations that decrease the reliability of quantifying cells in the anterior chamber by laser photometry compared to slit-lamp cell evaluation. The instrument still examines a small volume, not the whole anterior chamber, and cells may escape detection at low grades. Reliable measurements may not be obtained in high grade of cells either, because aggregates of cells may prevent detection of individual peaks. As any large particle in the aqueous humor can produce a strong peak, inflammatory cells cannot be differentiated from other particulate matter such as pigment particles, debris, red blood cells or malignant cells [9].

An Ocular Flare Activity Meter (OFAM) uses an alternative measure to calculate flare values based on Rayleigh scattering rather than the Tyndall effect. Rayleigh scattering describes the physical scattering of light by small molecules and may be calculated from non-laser light sources by measuring the angle of scatter and response at several specific wavelengths. This method is fundamentally more sensitive than Tyndall methods in measuring concentration of small molecules in an aqueous medium [10]. Invernizzi and colleagues [11] reported that swept-source (SS) optical coherence tomography (OCT) of the anterior segment could be used for a comprehensive assessment of anterior chamber inflammation, providing objective measurements of inflammatory cells and aqueous flare [11]. The efficacy of new approaches to identifying BAB breakdown due to ocular inflammatory response is yet to be determined.

Laser flare photometry in health

Flare values as assessed by LFP have been found to increase slightly with age in healthy individuals. It may be related to a breakdown of the BAB, changes in protein composition of the aqueous humor or cataract development with age [5, 9, 12–14]. In a study of normal subjects by Guillén-Monterrubío and colleagues [15], the mean value

of the photon count/ms was 4.5. It was 3.0 in the age group of 10-19 years; 3.1 in the age group of 20-29 years; 3.5 in the age group of 30-39 years; 5.0 in the age group of 40-49 years; 4.8 in the age group of 50-59 years; 5.6 in the age group of 60-69 years; 5.8 in the age group of 70-79 years; and 11.5 in the age group of 80 years or older [15]. Tugal-Tutkun and colleagues [9] reported that aqueous flare intensity was found in the range of 2.9–3.9 ph/ms in healthy individuals between 20 and 40 years of age, and 5.0–6.5 ph/ms in healthy individuals between 70 and 80 years of age [9].

Factors influencing the measurement of laser flare photometry are cataract, corneal opacity, pupil size, intraocular lens and shallow anterior chamber [16]. A decrease in photon count/ms with pupillary dilatation after mydriatic instillation has been reported, possibly due to pharmacological effects of mydriatic agents or reduced reflection of light by the iris [5, 12–14, 17].

A study by Hasanreisoglu et al [18] evaluated effects of maximal anterior cortical lens density on laser flare photometry and concluded that the back-scattered light from anterior cortical lens could affect laser flare photometry measurements. It is still a matter of discussion whether or not lens opacities significantly alter the results of aqueous flare measurements with a laser flare-cell meter [19, 20]. Circadian variations in laser flare photometry measurements have been observed, with higher values in the morning than in the evening [21]. No significant difference in photon count/ms (aqueous flare) was found to exist between right and left eyes, between sexes, or between irides of different color in healthy individuals [14, 15]. An occasional cell was found in 10.4%-59% of normal eyes [14, 15]. Effects of several ocular drugs over laser flare photometry readings have been reported. The major drug-related effect occurs as an increase in flare value after usage of anti-glaucomatous medication, which is due to a decrease in aqueous volume and subsequent increase in the aqueous protein concentration [7].

Laser flare photometry in disease

Increased levels of aqueous flare intensity caused by BAB breakdown are seen in eyes with anterior or posterior segment inflammation [22–24]. LFP was accurate in monitoring response to therapy for anterior segment inflammation in acute HLA-B27-related anterior uveitis. In a study of 44 patients presenting with an acute episode [23], mean initial flare was 160 ± 22 ph/ms (range: 11–787 ph/ms) compared to 4.7 ± 0.16 ph/ms in controls. All patients were given standard therapy of hourly instillations of 1% prednisolone drops progressively tapered after 3 days according to evolution of inflammation. A 50 and 90% flare reduction occurred after 2 and 8 days, respectively, under the standard therapeutic regimen used. Following periocular injection of betamethasone 4 mg, a 50% flare reduction occurred between 10 and 24 h. A flare level under 8 ph/ms was accepted as the end of an episode [23]. In a study of anterior chamber uveitis by Bernasconi and colleagues [8], mean initial flare was 143 ± 23.9 ph/ms, and a 50 and 90% flare reduction occurred after 3.9 and 19.6 days, respectively, under the standard therapeutic regimen used. LFP was significantly more sensitive for both 50% and 90% flare reduction in assessing the decrease of anterior chamber inflammation. LFP was superior to slit-lamp cell evaluation in monitoring anterior chamber inflammation in uveitis. Nevertheless, it is believed that flare, becoming a quantitative parameter when measured by LFP, rather than cells, should be considered the gold standard to measure anterior chamber inflammation in uveitis.

There have been also reports on the use of LFP in monitoring response to therapy for posterior segment inflammation in Behçet uveitis [22, 24–26]. In a study by Guex-Crosier and colleagues [22], mean pretreatment flare was found to be 331.8 ± 47.7 ph/ms compared to 4.7 ± 0.16 ph/ms in healthy individuals. A significant flare decrease was observed after initiation of corticosteroid treatment in patients with Behçet uveitis. During the follow-up of these patients, each time a flare rise of more than 20% of the lowest value was seen, it was always followed by a recurrence of uveitis [22]. Tugal-Tutkun and colleagues reported that mean flare levels during active periods of Behcet's uveitis were 62.5 ± 126.8 ph/ms. Mean flare in patients in clinical remission was significantly higher than in healthy controls (6.8 ± 4.2 ph/ms versus 3.7 ± 0.7 ph/ms) and flare readings showed a significant correlation with fluorescein angiographic leakage scored by a masked observer. Flare values showed a significant correlation with all clinical scores of intraocular inflammation, including the grade of anterior chamber cells at the slit lamp, vitreous haze, and the number of active fundus lesions. Concomitant breakdown of the anterior blood–ocular barrier (blood–aqueous barrier) may be producing a subclinical flare rise in posterior uveitic entities. A subclinical flare rise was not found in Behçet uveitis patients without ocular involvement, and mean flare was not found to be significantly different between patients without ocular involvement and healthy controls [25]. Yalcindag and colleagues [24] evaluated the association between intraocular inflammation and laser flare photometry measurements in Behçet uveitis. The flare levels were compared with the grade of anterior chamber cells, the presence of vitreous cells, the complications of uveitis, and fluorescein angiography scores. The median LFP-flare was 8.4 ph/ms (range: 6.67-16.47 ph/ms) in the uveitis attack group, 4.85 ph/ms (range: 3.85-10.62 ph/ms) in the angiographic remission group and 2.8 ph/ms (range: 2.35–4.83 ph/ms) in controls. Flare values correlated with the degrees of both anterior chamber and vitreous inflammation and with angiographic scoring. Yalcindag and colleagues [24] concluded that LFP may reduce the necessity of fluorescein angiography in monitoring subclinical inflammation and may be an indicator of posterior segment activity when fluorescein angiography is not applicable [24].

Studies reported on the use of LFP for the assessment of BAB disruption in Vogt–Koyanagi–Harada (VKH) disease, a disorder characterized by bilateral granulomatous uveitis, mostly with posterior pole lesions in the form of chorioretinitis and exudative retinal detachment [27–30]. In a study by Fang and colleagues [28], before treatment, in initial-onset and recurrent VKH eyes, mean aqueous flare were 8.1 vs 43.6 ph/ms, and mean cell counts were 2.0 vs 39.4 cells/0.5 mm^3, whereas in control eyes, mean aqueous flare were 4.7 ph/ms, and mean cell counts were 0.6 cells/0.5 mm^3. Patients with initial-onset VKH disease typically showed severe diffuse choroiditis, exudative retinal detachment and optic disk edema with or without minor involvement of anterior segment, whereas patients with recurrent VKH disease manifested as severe granulomatous anterior uveitis in association with ''sun-set glow'' fundus and Dalen–Fuchs nodules. Patients with recurrent VKH disease displayed much higher aqueous flare values and cell counts at uveitis onset and a gradual recovery of these two parameters following immunosuppressive treatment. Fang and colleagues [28] concluded that recurrent VKH patients displayed a more striking and long-lasting breakdown of the BAB and more severe inflammation than initial-onset VKH patients. Maruyama and colleagues [29] aimed to assess changes in flare values in patients treated for VKH disease. They found that mean flare values changed from 24.03 ph/ms before treatment to 8.91 ph/ms at day 60 of treatment. They also found that patients with recurrent VKH disease had higher initial flare number than patients with nonrecurrent VKH disease requiring steroid therapy only (24.68 ph/ms vs 14.16 ph/ms, respectively). In addition, they concluded that flare number during the initial phase may be useful in determining the prognosis for VKH disease and choosing therapeutic options. LFP can be a useful tool that helps in monitoring subclinical inflammation in cases with chronic VKH. In a study by Morata and colleagues [30], although clinical ocular inflammation was observed only in 4 eyes (11.8%), inflammatory signs were observed in 23 out of 34 eyes by LFP (67.6%), in 27 eyes by indocyanine green angiography (79.4%), and in 10 eyes by enhanced depth imaging optical coherence tomography (EDI-OCT) (29.4%).

Juvenile idiopathic arthritis (JIA)-associated uveitis is characterized by a prolonged chronic course, and is often treated suboptimally if LFP is not used for flare monitoring. Tugal-Tutkun and Herbort [31] reported that a group of patients with a deleterious evolution and complications were found to have a much higher mean initial flare of 184.98 ± 97.04 ph/ms with a suboptimal reduction after maximal therapy to 106.1 ± 82.31ph/ms (42.5% reduction) as compared with the group with favorable outcome whose initial flare was much lower (69.81 ± 89.64 ph/ms) and who responded well to maximal therapy with a reduction of flare to 24.94 ± 21.37 ph/ms (65% reduction). Others [32] concluded that high LF values (> 20 ph/ms) in patients with JIA uveitis are associated with poor vision and a higher prevalence of uveitis complications.

A study by Guex-Crosier and colleagues [22] confirmed LFP evidence of a relatively mild disruption of the BOB in patients with pars-planitis or sarcoidosis-associated posterior uveitis, whereas LFP flare values in toxoplasmosis or in birdshot chorioretinopathy were close to the norm. In a study by Biziorek and colleagues [33], mean initial flare was pronounced in multifocal choroiditis and panuveitis, HLA-B27 positive acute anterior uveitis, and acute herpes zoster anterior uveitis, and mild to moderate in Fuchs uveitis syndrome, pars planitis, and posterior uveitis in toxoplasmosis.

LFP studies have also displayed an increase in aqueous flare values in a variety of non-inflammatory posterior segment disorders such as diabetic retinopathy [34], retinal vein occlusion [35], age-related macular degeneration [36], retinitis pigmentosa [37] and choroidal melanoma [38].

Breakdown of the BAB was found to precede the development of retinopathy in patients with diabetes mellitus. In diabetic patients without diabetic retinopathy (DR), aqueous flare values as measured by LFP were higher than in control eyes of healthy individuals. In patients with proliferative DR (PDR), aqueous flare values as measured by LFP (17.34 ph/ms) were significantly higher than in diabetic patients without DR (12.03 ph/ms), patients with non-proliferative DR (12.69 ph/ms), and patients with diabetic maculopathy (13.81 ph/ms) [39]. Others [40] also demonstrated an increase in aqueous flare values (as measured by LFP) with progression of DR. In patients with PDR, there was an increase in LFP flare values at early time points after panretinal laser photocoagulation (16.66 ph/ms at baseline, and 19.44 ph/ms at one hour and 18.53 ph/ms at 24 hours) [41]. In eyes that had undergone successful retinal laser photocoagulation and showed confirmed regression of neovascularization, there were still increased LFP flare values compared to diabetic eyes without DR. There was no significant difference in LFP flare values between these eyes and eyes with PDR or active retinal neovascularization [39]. In studies of patients with diabetic retinopathy and retinal vein occlusion, correlations were found between LFP flare values and fluorescein angiography parameter values [35, 42].

In eyes with choroidal melanoma, a significant flare increase correlating with the tumor size has been shown when compared with the normal fellow eyes [38]. In eyes with very large melanomas (with a diameter >20 mm and/or a height >10 mm), the mean anterior chamber flare (23.8 ph/ms) was significantly higher than in eyes with medium and large melanomas (with a diameter of 10-20 mm and a height of 3-10 mm; 15.9 ph/ms). In addition, in the latter eyes, the mean anterior chamber flare was higher than in eyes with small melanomas (with a diameter of less than 10 mm and a height of less than 3 mm; 7.8 ph/ms). In all three studied groups, the absolute flare values

were significantly higher in the tumorous eye than in the healthy eye.

LFP has been successfully used to assess BAB breakdown caused by surgical trauma of the eye associated with cataract surgery [43, 44], glaucoma [45, 46], rhegmatogenous retinal detachment [47, 48], or keratoplasty [49, 50]. De Maria and colleagues [51] believe that the quantitative analysis of intraocular inflammation by laser flare and cell photometry after cataract surgery might be a tool to predict the risk of pseudophakic cystoid macular edema.

Others [52, 53] used LFP data for assessing the efficacy of postoperative anti-inflammatory and anti-bacterial therapy. Fardeau and colleagues [54] believe that early detection of an increase in flare could lead to a close follow-up of patients with chronic pseudophakic endophthalmitis following cataract surgery, with the prompt modification of therapeutic intervention contributing to the preservation of a favorable visual outcome.

There have been reports [55–57] on changes in LFP data after intravitreal antiangiogenic therapy. Lages and colleagues [58] aimed to evaluate the utility of laser flare photometry in monitoring inflammation after intravitreal injection of anti-vascular endothelial growth factor agents, particularly to detect early stage post-injection endophthalmitis. Of the 736 injections included in the study, 705 cases (95.8%) had a post-injection flare at 72 h ≤ 30 ph/ms, 29 cases (3.9%) had a post-injection flare at 72 h between > 30 and 50 ph/ms, and 2 cases (0.3%) had a post-injection flare at 72 h above > 50 ph/ms (664 and 742 ph/ms). These latter two cases were diagnosed as early-stage endophthalmitis. Lages and colleagues [58] concluded that LFP is a cost-effective method of screening for early stage post-injection endophthalmitis, and values > 50 ph/ms 72-h post-injection should prompt immediate evaluation by an ophthalmologist.

Therefore, changes in LFP flare values are a reliable biomarker of the state of the BAB in patients with uveitis, diabetic retinopathy, and other ocular disorders. We hypothesize that the use of LFP flare in combination with other ocular vascular biomarkers available for quantitative analysis (ocular surface temperature [59, 60], ophthalmic heat flux density [61, 62], retinal vascular biomarkers imaged by adaptive optics ophthalmoscopy [63, 64] and choroidal vascular biomarkers imaged by OCT [65]) can improve the efficacy of early eye disease diagnosis, including the diagnosis at the subclinical stage.

Conclusion

The LFP technique is a non-invasive and objective method for assessing BAB breakdown in patients with ocular inflammation of the anterior or posterior segment as well as those with non-inflammatory disorders. The method allows reliable detection of such biomarkers of the state of the BAB as the intensity of the scattered light (flare) and number of cells in the aqueous of the anterior chamber. LFP improves the capability for early eye disease diagnosis and objective monitoring of patients treated for some ocular and systemic disorders. LFP monitoring enables the opportunity for predicting disease development and facilitates prompt modifications in therapy.

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Disclosures

Received 04.07.2023

Accepted 31.07.2023

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Author Contributions: *The authors confirm the following contributions to the article: study conception and design: NVP; data collection and analysis: OSZ, OED, OVZ, ARK, and KVT; drafting of the manuscript: OZ. All authors read and approved the final manuscript.*

Funding sources: *This research received no special grant from any funding agency in the public, commercial, or non-for-profit sectors.*

Conflict of interest: *All authors have read the journal's Author Agreement and Conflict of Interest policy. The authors have no potential conflict of interest to declare.*

Abbreviations: *BAB, blood-aqueous barrier; BOB, blood–ocular barrier; DR, diabetic retinopathy; JIA, juvenile idiopathic arthritis; LFP, laser flare (cell) photometry; VKH, Vogt–Koyanagi–Harada*