CURRENT CLINICAL APPLICATION OF MICROPERIMETRY: A REVIEW

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ABSTRACT

Microperimetry (MP) is a technology that allows the study of retinal sensitivity at different foveal and parafoveal areas as well as eye fixation. It is a technique of functional evaluation, providing a direct correlation between anatomical and functional outcomes. There are a great variety of studies published not only evaluating the repeatability or reliability of measurements obtained with this technology but also describing and exploring different clinical applications. MP has been shown to be useful in the characterization of sensory and motor conditions, such as amblyopia or nystagmus. Concerning ocular pathology, different studies have confirmed the usefulness of MP for evaluating and analysing different retinal pathological conditions, such as age-related macular degeneration or glaucoma, and to analyze the effect of different medical or surgical treatments for these conditions. MP has been also shown to be useful for visual training or rehabilitation in some specific cases.

KEYWORDS: microperimetry, eye fixation, retinal sensitivity, visual rehabilitation, amblyopia, nystagmus

INTRODUCTION

Microperimetry (MP) is a technique that allows us to analyse different parts of the retina and simultaneously to assess how they respond to light stimuli, combining the anatomical and functional assessment of the retina in a same instrument.[1-3] MP allows the clinician to visualize the retina of the patient with an optical illumination system that projects light to the retina and a camera capturing an image which can be recorded by means of different software systems in a similar manner as other techniques of exploration of the eye fundus (Figure 1A). Likewise, a microperimeter projects light stimuli of different intensities to the retina to assess the sensitivity of each region and records the patient's responses to these stimuli, as other techniques of automated perimetry (Figure 1B). MP does not differ greatly from other techniques of ophthalmoscopy or perimetry, but provides the unique feature of allowing the performance of both exams in a single measurement, integrating both viewing and projection systems in a single instrument (Figure 1C).

Since the release of the first microperimeter, the SLO (Rodenstock),[4] the technique has maintained the same principles but has technologically evolved into more sophisticated models that are currently available, such as the MP1 (Nidek),[5,6] the OCT/SLO (Optos)[7] and the more recent of them, the MAIA system (Centervue).[8] The present review describes the main clinical applications of MP considering the scientific evidence reported in the last years. The applications of sensitivity and eye fixation evaluation with MP have been revised, with analysis of the specific uses in different conditions and diseases.

SENSITIVITY EXAM

Anatomical-functional correlation

The ability to locate the patient functional deficits in its own retina has been a breakthrough in the study of eye diseases. The last microperimeters even incorporate the possibility of correlating sensitivity with tomographic findings, either in a single acquisition, as the OCT/SLO system, or after acquiring both examinations separately and overlapping them later using specific software, as the MP1 and MAIA systems. Another advantage that provides MP with respect to other functional techniques is that although the size of the stimuli that are projected on the retina of the patient is the same compared to conventional perimetry, the region evaluated is much smaller, allowing the clinician to better examine in detail one specific region of the retina due to the shorter distance between stimulus.

Control of fixation losses

MP offers the correction of subject eye movements to generate an accurate projection of the light stimuli in the specific region that is going to be examined. This is possible due to the use of eye trackers. These eye trackers detect the position of the retina using as references some anatomical features, such as the position of a vessel or the size of the optic nerve, and generate automatically a recalculation of the new position where the light stimulus must be projected when there is a shift of the position of the reference image. This guarantees a correct projection of stimuli on the retina of the patient, being independent from fixation losses occurring during the test and therefore providing more reliable results.

Follow-up

The correct follow-up of a condition along different sessions is a consequence of the two previous characteristics: the measurement of the correlation between patient's retina and its sensitivity, and the confidence that this correlation analysis is good and reliable due to the control of fixation losses. Regarding the use of MP of follow-up, the instrument projects light stimuli in the same regions of the retina than in the previous visits, allowing the comparison of the variation in the results point-by-point.

FIXATION EXAM

Another important feature provided by MP is the possibility of studying the fixation of the patient in a form never studied with any other technique. During examination, eye trackers correct fixation losses of the patient by registration of eye movements, but at the same time these records provide us information of how is the eye fixating. In other words, MP allows the clinician to evaluate the stability and position of the fixation.

Fixation stability

The control of fixation losses provides an indirect measure of the position of the retina and their movements during the performance of the exam. This measure, which was initially used for obtaining more reliable perimeter examinations, provides valuable information about the ability of the subject to keep the eyes fixating at a point, and therefore about the stability of fixation. Fixation stability analysis can be done using two parameters, indexes P1 and P2, which indicates the percentage of points that are inside of a circle of 1 ° and 2 ° of radius, respectively, or by using the Bivariate Contour

Ellipse Area (BCEA), which represents the area of an ellipse which contains all points of fixation (Figure 2).

Position of fixation

The stability of fixation provides information on how stable or unstable is the eye position during the test, but also, depending on the region of retina that use the subject to focus his gaze, named as Preferred Retinal Locus (PRL), the clinician can detect if there is a central (when the PRL is foveolar) or eccentric (when using another region) eye fixation.

Visual rehabilitation

Visual rehabilitation through training of fixation is another innovation that incorporates MP. This consists on the use of acoustic signals to re-educate subject's fixation while looking at a fixating point with the MP device. This rehabilitation can be done in the same position of its PRL with the objective of working its stability or in another position of the retina when the objective is to create a new PRL with better sensory conditions.

CLINICAL APPLICATIONS

Sensory and motor conditions

MP was focused some years ago almost exclusively on the study of macular pathology and low vision, but in the most recent years more studies are being published showing the application of MP in other fields, such as binocular vision and evaluation of oculomotor problems.

Amblyopia

Regardless of whether amblyopia is due to sensory or motor deficits, the possibility of evaluating retinal sensitivity and fixation with MP, makes this technology useful for the evaluation of amblyopia. There is not only a decrease in the retinal sensitivity of the amblyopic eye that can be detected with MP, this instrument also allows the clinician to detect small central asymptomatic scotomas that are hardly detectable with other techniques.[9,10]

The study of fixation in subjects with amblyopia by means of MP has been reported in the peer-reviewed literature for both strabismic or anisometropic amblyopia.[10,11] Regarding the fixation pattern of the amblyopic and dominant eye, some authors have reported significant differences but only for subjects with strabismic amblyopia.[11] Likewise, the study of the eye fixation has been also used to correlate its stability and position with other clinical parameters, such as best corrected visual acuity (BCVA),[9-11] stereopsis,[11] or magnitude of strabismus.[10]

Nystagmus

Methods of recording ocular movements can be divided into electrophysiological methods, based on the analysis of bioelectrical properties of the eye, oculographic methods, based on the physical registration of eye positions over time, and other video eye trackers based on other different technologies. MP belongs to the second group with the advantage that allows the registration of eye movements directly on retinal image. For this reason, some authors have seen in MP an opportunity for the study of eye movements in nystagmus.[12-14] Our research group was the first that proposed the use of MP as an objective method of quantification of the nystagmic movement and characterization of fixation pattern in comparison to the video-

oculography.[12] Subsequently, we studied the fixation through MP in a group of subjects with nystagmus of different etiology with the objective of characterizing the different fixation patterns that can be present in this type of oculomotor condition.[13] A significant correlation was found in this study between retinal sensitivity and BCVA as well as between stability of fixation and BCVA.[13] In addition to studies related to subjects with nystagmus, other authors have studied the nystagmic movements associated with other conditions as is the case of oculocutaneous albinism,[15,16] even showing the possibility of fixation training in these subjects using MP.[16] It should be considered that although MP allows a characterization of fixation movements, MP software is not yet designed to extract the periodic aspects of nystagmus, as can be done with video-oculography system. MP allows us to characterize the movement directly on retina, but further studies are still needed to develop future applications for a more precise analysis of nystagmic movements.

Ocular pathology

MP is an instrument that has been mainly used to evaluate the impact on the visual function of different ocular pathologies or to monitor the follow-up of these pathological conditions. The usefulness of MP for the characterization of the eye fixation in pathological subjects has been also demonstrated in studies evaluating the fixation stability, the central or eccentric position of the PRLs, or the correlation between fixation and other clinical parameters, such as visual acuity, retinal anatomy or contrast sensitivity. In the following lines, we describe the clinical application of MP in some pathological conditions according to the peer-reviewed literature of the last years.

Age-related macular degeneration

MP has shown its utility in age-related macular degeneration (AMD). AMD has been studied by MP with different objectives: correlation of anatomical findings with functional deficits,[17-19] follow-up of the pathology over time,[20,21] pre and post-medical control[22,23] or control of a surgical treatment,[24,25] the study of eye fixation,[26,27] and performance of visual rehabilitation programs.[28] The possibility of correlating the anatomical and functional findings with MP has allowed the clinician to assess the level of loss of retinal sensitivity associated to different structural damages and to know which retinal layers generate a more significant damage on the visual function. Several authors have studied the relationship between retinal sensitivity and the thickness of various layers, such as the retinal pigment epithelium (RPE) or the outer segment of photoreceptors.[18,19] Other authors have also studied the fixation depending on the stage of the disease. Although these authors have found a direct correlation between the initial and intermediate phases of AMD and sensitivity, no correlation has been observed between AMD stage and fixation.[17]

Regarding the follow-up of AMD, some authors have recommended to perform a first measure of training before the definitive measurement as significant differences in intrasession test-retest variability is present in subjects with AMD[20] in contrast to normal subjects.[8] After the baseline examination, several authors have analysed longer variations in MP outcomes in order to assess whether the technique is useful for the monitoring of the evolution of the disease, with a significant sensitivity loss during one year of evolution,[21,22] without BCVA changes associated.[20] In the case of fixation, no significant differences in the evolution of the pathology during a 1-year follow-up have been detected.[21] More studies are needed to confirm this trend in a longer term.

An accurate sensitivity measure with MP may allow a precise correlation over time between examinations, with the potential of being useful in the control of anatomical changes that may occur as a consequence of the evolution of the pathology, as mentioned before, or after medical[22,23] or surgical treatments.[24,25] Some authors have studied by MP the improvements in retinal sensitivity produced after medical treatment, as for example, in the case of intravitreal anti–vascular endothelial growth factor (anti-VEGF) therapy[22] or after long term prescription of supplementation of lutein and zeaxanthin.[23] In the case of surgical treatments, MP has also demonstrated its usefulness for comparisons pre and post-surgery,[24] and in some cases for the long term follow-up of the results of different surgical techniques, such as the autologous translocation of choroid and retinal pigment epithelium.[25]

The study of fixation in AMD has been based, as in other pathologies that affect central vision, not only in the study of stability but also in centrality.[27,29,49] In the case of stability, this has been studied by means of the BCEA, correlating the instability of the fixation with the further evolution of the pathology[26] or the lower speed of reading.[29] The identification of PRLs and their eccentricity from the fovea will determine, combined with the study of BCVA, the region of the retina that is the most suitable for observation by the patient.[27] Also, if the patient has not developed an optimal PRL by himself, visual training module allow patients to locate and train that region with greater functional possibilities.[28]

Most of studies agree in the statement that the structural damage precedes the loss of BCVA, and evidence that the evaluation of visual acuity in AMD is not enough to assess the visual function affectation, being necessary an additional functional testing. In this way, MP is very useful because it can detect these small losses of functionality that are present in the early stages of AMD.[17,18,20]

Diabetes

Besides AMD, diabetes is the most studied pathology by MP, probably due to its significant incidence in the general population, but also because MP provides a comprehensive and precise examination of sensitivity in diabetic vascular problems. Different MP applications have been described in the peer-reviewed literature for diabetic patients, such as the characterization of anatomical and functional changes,[30-34] comparison of pre and post-medical or surgical treatment,[35-41] or the study of eye fixation.[30,42] The characterization of anatomical and functional changes in diabetes through MP differs from the study of sensitivity losses caused by ischemia due to capillary drop-off,[30] the loss of sensitivity in macular-induced diabetic edema,[31,32] or the study of anatomical alterations as microcysts[32,33] or hard exudates.[32,34]

There are multiple medical treatments for diabetic retinopathy. Some of them have been analysed by MP in order to evaluate the changes before and after their prescription, such as flavonoids and vitamins,[35,36] anti-VEGF injections,[37,38] or dexamethasone implants,[39] as well as to evaluate the follow-up of the effect of these treatments over time.[35,39] MP has been also used to study some surgical treatments, such as pan-retinal laser photocoagulation, with the objective of quantifying the reduction on sensitivity[40] and to compare several of them.[37,41]

Regarding the stability and location of fixation, a correlation between the stability of fixation and other parameters, such as BCVA,[30,42] the presence of central scotomas,[42] or anatomical findings has been detected.[42] Also, the correlation between the location of fixation and anatomical findings has been studied[42] as well as the relationship between fixation stability and PRL location.[42]

Macular hole

Macular hole (MH) is the third pathological condition with more studies using MP as it is a pathology in which an exact correlation between functionality and anatomy is almost indispensable for clinicians and practitioners. There are many studies on the correlation of anatomy and functionality, such as those studying the relation between sensitivity and depth of the hole[43] or the integrity of the different layers of the retina as the external limiting membrane[44] or the photoreceptors.[43,44] Most of studies with MP in MH are focused on assessing the patient's characteristics prior to surgery. Specifically, there are studies aimed at predicting the surgical results of MH,[45,46] comparing the sensitivity and fixation improvements before and after surgery,[47] or comparing the results with different surgical techniques.[48] Also, the possibility of visual rehabilitation by means of MP has been studied following surgery in MH to improve the results of BCVA.[49]

Central serous corioretinopathy (CSC)

Authors have mainly studied the anatomical-functional correlation in CSC (retinal thickness/sensitivity), relating those regions with loss of the ellipsoid portion of the inner segments with decreased sensitivity[50] or studying the concordance between angiography and the sensitivity obtained through MP.[51] Concerning the treatment of CSC, MP provide the clinician information about results obtained by photodynamic therapy through the analysis of pre and post-surgical sensitivity,[52] or about which technique provides the best results in terms of sensitivity in CSC patients.[53,54]

Glaucoma

Glaucoma is a condition that mainly affects peripheral vision and only it is perceived by patient in the more advanced stages, when the central or paracentral vision is affected. Conventional perimetry has become the gold standard technique in the detection of the glaucomatous damage, but MP can also be a valuable tool in the assessment of glaucomatous patients. There are different studies comparing MP and conventional perimetry outcomes that reveal that MP seems to be more sensitive in predicting glaucomatous visual field loss.[55] Some authors suggest that this is because the measure of the macular thickness is also comparable to the quantification of the glaucomatous damage of the peripapillary nerve fiber layer.[56] Therefore, if changes in macular structure correlate with functional alterations,[57,58] the measure of functional deficits at the macular level may also reflect the glaucomatous damage.[56] There are some studies on the use of MP in patients with glaucoma with different purposes: to correlate the anatomy with the functionality,[57,58] to analyse the differences between open-angle and close-angle type glaucoma,[56] to compare the results with conventional perimetry,[55,57] to study the fixation pattern,[59] and to evaluate of potential of rehabilitation with MP through biofeedback.[59,60]

Rod-cone alterations

In rod and cone dystrophies and degenerations, which are pathologies affecting directly photoreceptors, functional techniques are very useful in measuring the light response because deficiency can be determined according to the decrease in the answers of patients. In this sense, MP does not seem to have much to contribute to the rest of the studies carried out with conventional perimetry, but it has the advantage of correlating sensitivity losses with anatomical changes.

Stargardt disease

Stargardt disease is a degenerative disease that affects the photoreceptors of the macula. MP is very useful in this pathological condition because it can characterize the macular damage through the loss of retinal sensitivity, and correlate it with anatomical findings.[61,62] Likewise, MP is a valuable technique for the study and monitoring of Stargardt disease over years.[61] MP has also shown its utility in the study of the fixation of subjects with Stargardt,[61,62] with some studies even showing the potentiality of visual rehabilitation with MP through fixation training.[63]

Retinitis pigmentosa

Retinitis pigmentosa (RP) comprises a group of retinal dystrophies with different clinical signs that primarily affect the rods, but also with some involvement of cones. While classically RP is a pathology that affects to the middle retinal periphery, this pathological condition continues its expansion towards the central region, generating a small central island of vision in its more advanced phases. MP is very useful to quantify this remaining central visual field as visual acuity can be preserved,[64] but it is insufficient to quantify the true deficit of RP patients. A more functional analysis, as the measure of retinal sensitivity, is needed to assess the progress of the pathology.[64]

Epiretinal membrane

The epiretinal membrane (MER) or macular pucker is a growth of tissue in the vitreoretinal interface that can cause macular damage due to the traction that generates on the retinal surface. It usually occurs near or in the macula, causing the presence of metamorphopsias as well as a decrease in BCVA. However, BCVA is not a reliable indicator of the impairment of visual function, because MERs are composed of

translucent tissue that also produces a decrease in contrast sensitivity.[65] MER treatment is surgical and has the associated risk of producing central scotomas caused by retinal traction during the intervention. MP is an ideal instrument for the characterization of the visual functional changes in MER, as it does not only assess the visual loss prior to surgery,[65] but also it allows the clinician to perform a detailed comparative analysis pre and post-surgery,[66] an analysis subsequent to the intervention,[67] and a control and monitoring of results over time.[66,67] The majority of studies with MP are based on the analysis of the outcomes of the surgical treatment of MER, although some authors have also studied the fixation pattern in subjects with MER.[68]

Toxicity

MP has been a breakthrough in the characterization of macular pathologies that affect to a very specific retinal areas, such as toxic maculopathies induced as a side effect of different medications prescribed for the treatment of systemic diseases. These toxic alterations sometimes remain unnoticed and undetectable by other techniques such as conventional perimetry.[69] It is the case of chloroquine and hydroxychloroquine maculopathies[69,70] induced by medications used for the treatment of rheumatoid arthritis or lupus, or deferoxamine maculopathy,[71] an agent used to treat systemic iron overload. Besides these toxic effects, there are other substances that are used in surgical procedures and that produce toxicity of retinal tissues, such as perfluorocarbon liquid[72] or brilliant blue G.[73]

Conclusions

MP is a technique that allows to correlate retinal anatomical findings and functional outcomes as well as to study the eye fixation of a patient. Therefore, it is a crucial tool for evaluating and understanding the causes of functional loss in different retinal conditions. Furthermore, MP allows the clinician to understand how the patient is using the macular area for his/her vision, with the possibility of characterizing the pattern of fixation and even to train the fixation to improve the visual acuity and binocular vision. There are a very extensive peer-reviewed literature demonstrating the clinical applications of MP in the study of sensory and motor conditions, such as amblyopia or nystagmus, as well as in the evaluation of different ocular pathologies, such as ARMD, diabetic retinopathy, MH or toxic retinopathies and the effect of different therapeutic approaches for their treatment. More studies are still needed to define more future potential applications of this technology as well as to develop the potential of MP as a tool for visual rehabilitation and training.

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FIGURE LEGENDS

Figure 1.- Fundus image obtained with SLO from left eye of a normal subject (A); Sensitivity exam from left eye of a normal subject (B); both sensitivity exam and fundus image obtained with SLO from left eye of a normal subject (C). All images were obtained from the same patient with MAIA microperimeter (Centervue).

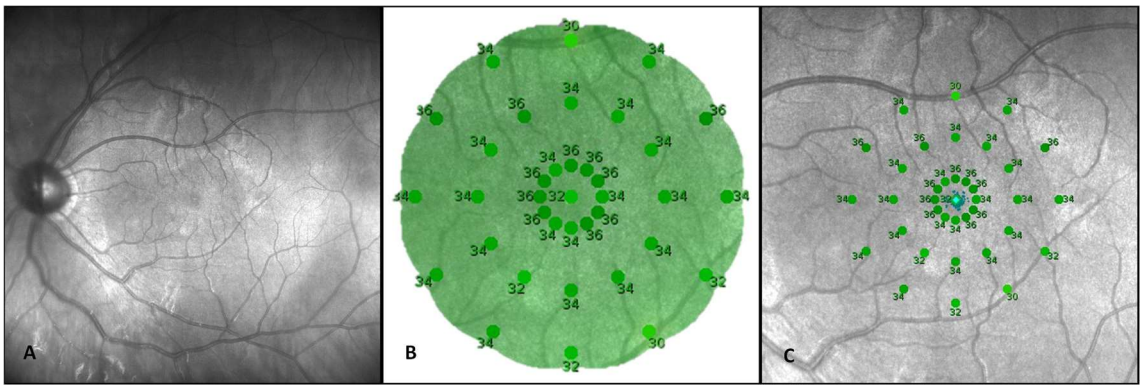
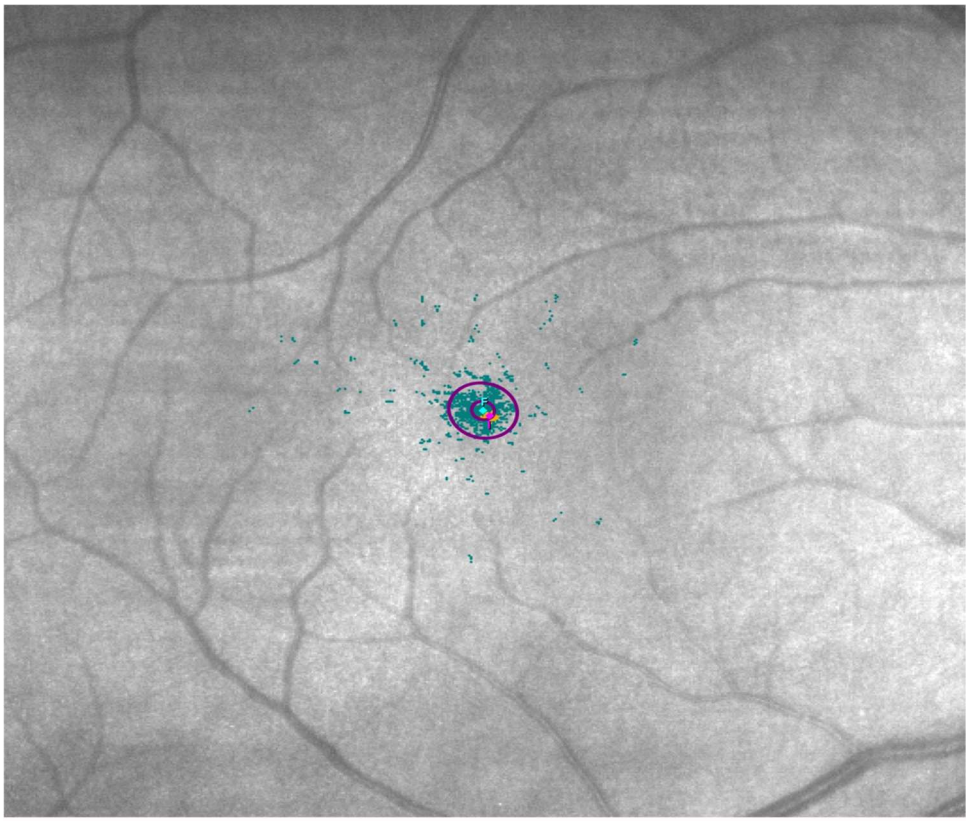


Figure 2.- Fixation exam obtained from a normal subject with stable fixation obtained with the MAIA microperimeter from Centervue. Blue points represent all the positions, fixation points of the patient's eye during the examination. Purple ellipses represent Bivariate Contour Ellipse Areas (BCEA) with 95% of SD (standard deviation) and 63% of SD. Total area for each SD, horizontal and vertical diameter (H° x V°) in degrees of those ellipses and the angle of orientation are shown.



Bivariate Contour Ellipse Area:
63% BCEA: 0.4° x 0.4°, Area = 0.6°², angle = -29.5°
95% BCEA: 1.3° x 1.2°, Area = 5.1°², angle = -29.5°