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MAJOR REVIEW

Psychophysical Function in Age-related Maculopathy

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Abstract. Age-related macular degeneration (AMD), the late stage of age-related maculopathy (ARM), is the leading cause of blind registration in developed countries. The visual loss in AMD occurs due to dysfunction and death of photoreceptors (rods and cones) secondary to an atrophic or a neovascular event. The psychophysical tests of vision, which depend on the functional status of the photoreceptors, may detect subtle alterations in the macula before morphological fundus changes are apparent ophthalmoscopically, and before traditional measures of visual acuity exhibit deterioration, and may be a useful tool for assessing and monitoring patients with ARM. Furthermore, worsening of these visual functions over time may reflect disease progression, and some of these, alone or in combination with other parameters, may act as a prognostic indicator for identifying eyes at risk for developing neovascular AMD. Lastly, psychophysical tests often correlate with subjective and relatively undefined symptoms in patients with early ARM, and may reflect limitation of daily activities for ARM patients. However, clinical studies investigating psychophysical function have largely been cross-sectional in nature, with small sample sizes, and lack consistency in terms of the grading and classification of ARM. This article aims to comprehensively review the literature germane to psychophysical tests in ARM, and to furnish the reader with an insight into this complex area of research. (**Surv Ophthalmol** 54:167–210, 2009. © 2009 Elsevier Inc. All rights reserved.)

Key words. age-related maculopathy • color vision • hyperacuity • perimetry • psychophysical tests • Spatial vision • temporal function • visual adaptation

I. Introduction

Age-related macular degeneration (AMD), the advanced stage of age-related maculopathy (ARM), is a degenerative condition of the macula characterized by dysfunction and death of photoreceptors secondary to an atrophic (geographic atrophy, GA) and/or a neovascular (choroidal neovascularization, CNV) event. Currently, AMD is the leading cause of blind registration in the developed world,[73,113,119] with CNV accounting for 80–90% of these cases.[149,196]

In the future, the prevalence and incidence of ARM is expected to rise because of an increase in life expectancy, and the consequential demographic shift toward an elderly population will have implications for the socio-economic impact of this disease.[24,235] Furthermore, the currently available therapeutic interventions for this condition are aimed largely at preservation of presenting visual acuity (VA),[205,320,321,334] even though a significant proportion may achieve some visual gain with the newer vascular endothelial growth factor inhibition therapies.[125,332] Thus, complete restoration of vision remains an unrealistic goal at least within the next decade. Finally, the impact of ARM on the activities

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of daily living, self-care, emotional well-being and overall quality of life are important, and are related to disease severity.[57,88,92,179,298,354] Therefore prevention, delay, or arrestation of progression to the late manifestations of ARM, namely CNV and/or GA, represent the best means of limiting the impact of this degenerative disorder on visual health and quality of life in the elderly population.

The early stages of ARM are characterized by drusen and/or pigmentary changes of the retinal pigment epithelium (RPE), and herald the loss of normal retinal status and, consequentially, an increased risk for the development of CNV and/or GA. A number of investigators have reported, in a cross-sectional fashion, various morphological changes in the fundus, which may be associated with subsequent development of severe visual loss. The characteristics of drusen, such as large number and size, confluence, softness, and associated focal hyperpigmentation of the RPE, are associated with an increased risk for progression to the neovascular stage of this disease.[42,43,45,128,269,300] However, the overall predictive value of such morphological changes is low, possibly reflecting the high incidence of age-related fundus changes.[335] In addition, the relationship, if any, between morphological and functional changes in the retina in ARM remains unclear. For instance, in a recent study, the severity of functional deficits in short-wavelength sensitive resolution acuity did not correlate well with the severity of morphological changes in ARM.[25]

The early lesions of ARM may be associated with a decrease in VA of approximately two or fewer optotypes (i.e., letters) when compared with eyes without such lesions.[169] This level of visual deficit is neither clinically meaningful nor reliably detectable, given that the test–retest variability of a logMAR chart is between one and two lines.[18,257] In addition, such a level of visual deterioration may pass undetected using the conventional Snellen chart, suggesting, therefore, that VA, the standard test of visual function typically performed in the clinical setting, is inadequate for the assessment of functional deficit in early ARM, and is therefore of no prognostic value with respect to the risk for atrophic and/or neovascular changes.

Consequently, other psychophysical tests of vision, which reflect the functional status of the macula, may be useful tools for assessing and monitoring patients with early ARM, and may detect subtle alterations in the macula before morphological fundus changes are apparent ophthalmoscopically, and before traditional measures of VA exhibit deterioration. Indeed, psychophysical studies have demonstrated that several parameters of visual function, in particular contrast sensitivity, visual adaptation, central visual field, and colour discrimination, deteriorate in the early stages of ARM. Furthermore, longitudinal studies have shown that some of these parameters, in isolation or in combination, may be of predictive value with respect to the progression to CNV and/or GA with a good degree of sensitivity and specificity.

This article represents an evidence-based and comprehensive review of psychophysical function in ARM, with particular emphasis on identifying those parameters of visual function that may be of predictive value for disease progression.

II. Anatomy of the Macula

The macula lutea refers to a region of the posterior retina that measures approximately 5.5 mm in diameter, and is exquisitely specialized for central and color vision.[289] The macula differs from the rest of the retina by the presence of an exceptionally high density of neural elements and restricted blood supply.[247] Furthermore, one of the unique feature of the primate macula is the presence of xanthophylls, lutein (L) and zeaxanthin (Z), which provide its eponymous yellow color. Together, these two xanthophylls are referred to as macular pigment (MP).[35]

MP peaks in the central 1–2 degrees of the fovea, and declines to optically negligible levels by 5–10 degrees radial eccentricity, along with shoulders or flanking peaks around 0.7 degrees eccentricity.[94] Furthermore, Berendschot et al in a recent study examined the spatial distribution of MP in 53 normal subjects using a custom-built scanning laser ophthalmoscope (SLO), and they observed a distinct ring pattern at a mean distance of 0.7 degree of the fovea in approximately half of the subjects.[27] Additionally, in a few of these subjects, the optical density of MP was greater at the site of the ring pattern, when compared with the optical density of this pigment at the fovea.

It is important to note that, at the macula, L exists as a single stereoisomer, whereas Z subsists as two separate isomers, zeaxanthin (3R, 3′R) and meso-zeaxanthin (3R, 3′S). Furthermore, both isomers of Z are present in equal concentrations at the macula; however, only zeaxanthin (3R, 3′R) is typically derived from dietary sources.[180] It is proposed that a conversion mechanism exists in the retina, whereby L is isomerized to meso-zeaxanthin, and this observation may possibly explain the presence of meso-zeaxanthin in the retina despite its absence in a typical diet.

The macula may be further subdivided into four anatomical zones, originally defined by Polyak,[246] and named in relation to the fovea (fovea centralis).

The foveola, which is the innermost region of the macula, corresponds to the visual axis, and is characterized by a high density of cone photoreceptors, absence of retinal vasculature, and dominance of Midget pathways arising from these cones.[247] It is important to note that short wavelength sensitive cones, rods, ganglion cells, and all inner nuclear layer neurons are absent from the foveola. The surrounding fovea, in the form of a slope, represents a transition from the cone-dominated avascular foveola to a rod-dominated vascular parafovea.[247]

The parafovea is characterized by an increasing rod:cone ratio and ganglion cells, with a relatively low density of retinal vessels.[83,84] The outermost region, the perifovea, can be viewed as a transition zone between the highly specialized macula and the peripheral retina. The greater than average densities of cones and ganglion cells sets this zone apart from the retinal periphery, whereas a high rod:cone ratio (rod:cone ratio, 33–130:1), along with dense retinal vasculature, are two features common to the perifovea and the peripheral retina.[83,84]

III. Age-related Maculopathy: Definition

In this review article, we have, where possible and in the context of the grading system used in the cited studies, adopted the International Classification and Grading System for Age-Related Maculopathy and Age-Related Macular Degeneration.[30] According to this classification, early ARM is defined as the presence of soft drusen (≥63 μm) and/or areas of RPE changes in the form of hyperpigmentation and/or hypopigmentation. The late stages of ARM, also known as AMD, include dry AMD (GA of the RPE in the absence of neovascular AMD) or neovascular AMD (RPE detachment or CNV with or without its sequelae such as hemorrhagic detachment of either the RPE or neurosensory retina, presence of subretinal or sub-RPE hemorrhage or subretinal fibrosis). It is important to emphasize that in this classification, VA is not used to define the presence of ARM; however, a few of the cited studies have used the term pre-ARM to describe patients with early ARM and normal VA.[64,70]

IV. Age-related Maculopathy: Why the Macula?

The vulnerability of the macula to degenerative changes possibly reflects the anatomical and physiological features that render this region of the retina uniquely suitable for central vision.[247] The macula has a very high density of photoreceptors, which consume higher levels of oxygen than any other cell type in the body. However, and paradoxically, these cells have a restricted blood supply from the retina, and depend on the oxygen supplied by the choriocapillaris.[201] The blood flow within the choriocapillaris is controlled mainly by sympathetic innervation, and lacks metabolic autoregulatory capabilities.[93] In other words, the choroidal blood flow is independent of metabolism in the outer retina, and, therefore, is unable to alter blood flow in response to an increase in metabolic demand. Furthermore, with aging, there is a known decrease in the density and volume of the choriocapillaris, and a consequential reduction in the choroidal blood flow, thus rendering the macula exceptionally vulnerable to degenerative changes.

In addition, there are two adaptative mechanisms in young individuals to secure high diffusion of oxygen from the choroid to the macula photoreceptors per unit time, a wide caliber of the choriocapillaris vessels and a reduced thickness of the elastic lamina of Bruch's membrane.[67,120] However, and in the long term, these result in an accumulation of insoluble substances in Bruch's membrane and in the sub-RPE space, which then acts as a barrier to the effective diffusion of oxygen and nutrients to photoreceptors. Oxidative stress and an inflammatory response are the inevitable sequelae of such changes, thus promoting degenerative processes.

V. Visual Psychophysics

Visual psychophysics (psycho = perception, and physics = physical nature of the stimulus) is the science of studying visual perception and sensation by determining the relationship between controlled visual stimuli and a subject's response.[46] Assuming that the retina and brain are solely responsible for transforming light into vision, psychophysical studies provide valuable information about the functional status of visual processes. Furthermore, psychophysical findings are complementary to physiological studies.

The majority of the psychophysical tests are based on the concept of threshold testing, the threshold being defined as a point where a given visual stimulus may just be detectable or undetectable. It is important to note that humans are not perfect observers, and, therefore, thresholds are often defined in probabilistic terms. Furthermore, the investigator has a large degree of freedom to vary the stimulus patterns in space, time, brightness, and color. The method of adjustment, the method of limits, the modified methods of limits (staircase), and the method of constant stimuli represent just a few modes of presenting the stimulus during testing (Kalloniatis et al 2005; http://webvision.med.utah.edu).

During a psychophysical test, subjects are instructed to commit to an answer in order to minimize the variations in the obtained threshold. During the "Yes-No" segment, the subject judges the presence or absence of a given stimulus, whereas the "Forced Choice" procedure involves forcing the subject to choose among given alternative choices, one of which contains the correct response. A two-alternative force choice describes a subject choosing between two alternatives, and choosing from four and six alternatives are called 4- and 6-alternative forced choice test, respectively (Kalloniatis et al 2005; http://webvision.med.utah.edu).

The psychophysical functions when measured during scotopic conditions are mediated by the rods, and are associated with a relative insensitivity of the central retina when compared with the surrounding periphery. In contrast, during photopic conditions, the cone photoreceptors are involved in mediating vision, and the central retina usually becomes more sensitive than its surrounding retinal periphery. Furthermore, psychophysical tests assess rod and cone function simultaneously under mesopic conditions, and the sensitivities of the central and peripheral retina are equal under strict mesopic conditions.[204]

In this literature review, we have classified psychophysical function under five broad categories: spatial vision, temporal vision, visual adaptation, visual field testing, and chromatic function.

VI. Spatial Vision in Age-related Maculopathy

Spatial vision is the field of psychology that examines how the patterns of light on the retina are interpreted by the visual system (Ferwerda 2006; http://www.graphics.cornell.edu), and is further subdivided into VA (high-contrast VA), low-contrast VA, hyperacuity, reading speed, and contrast sensitivity.

A. VISUAL ACUITY

1. Definition and Basic Principle

Visual acuity, the acuteness of vision, is a measure of the spatial resolving ability of the visual system under conditions of very high contrast. In terms of contrast sensitivity (CS), VA is defined as a measure of the highest spatial frequency that can be detected at 100% contrast.[236] VA is the standard test of visual function, and is the most frequently used indicator of spatial vision in clinical practice and in clinical research studies.

Visual acuity may be considered as a three-stage hierarchical sequence,[313] which is represented graphically as a pyramid in Fig. 1. At the base of the pyramid lies the first stage of the visual process, and this involves detection of contrast. The second stage resolves that contrast into different elements by distinguishing various strokes, which comprise a letter or a symbol. Finally, the third stage consists of identification of a particular arrangement, such as a Snellen alphabet or symbols. Each stage has its own inherent limitations and the limitations of the previous stage. The detection stage is limited by optical attenuation (diffraction or aberration) and spatial summation by the neural receptive field (filtering), the resolution stage is limited by the spacing of receptive fields of visual neurons (sampling), and the identification stage is limited by several factors, such as attention, memory, and other cognitive functions.[313]

The third stage of the visual pyramid, the identification or recognition stage, is tested univer-

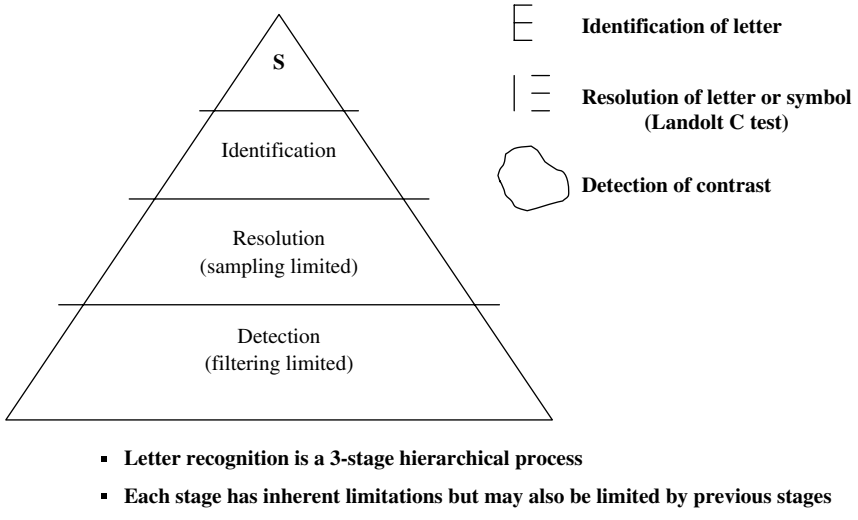

Fig. 1. The recognition pyramid: schematic representation of the process leading to letter recognition on visual acuity chart.

sally in the field of ophthalmology. If this stage of the visual pyramid is intact then we assume that every stage of the recognition process is functioning optimally, and that there is no need to test the individual layers of the pyramid.[313] When the recognition stage is measured for the purpose of research, the patient is encouraged to guess as he/she approaches his/her limit of resolution (forced choice methodology) in order to ensure that a threshold measure is recorded.

The Snellen optotype test chart, introduced by Herman Snellen in 1862, remains the most popular method of assessing VA in clinical practice.[151] The measured VA in Snellen fraction expresses the angular size of an optotype as a fraction, specifying the test distance as numerator and the distance at which the just resolvable optotype should be positioned in order to subtend an angle of 5 min of arc as the denominator.[151] The chart is familiar, quick, and easy to administer, and correlates reasonably well with the subjective description in most, but not all, subjects. However, there are number of flaws related to the design of this chart such as the crowding phenomenon, limited assessment of VA in patients with low vision, and inability to perform parametric tests with VA expressed in Snellen fraction.

An important advance in the measurement of VA came with the introduction of the logMAR distance acuity chart by Bailey-Lovie in 1976.[21] The logMAR designation expresses the VA as the common logarithm of the minimum angle of resolution (MAR), and with this notation 6/6 and 6/60 Snellen are represented by scores of 0 and 1.0 on the logMAR chart, respectively [Snellen fraction 6/6, MAR = 1, $\log_{10}$ (1.0) = 0; Snellen fraction 6/60, MAR = 10, $\log_{10}$ (10.0) = 1.0].[151] The Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart has emerged as the "test of choice" for measuring threshold acuity in vision research, and overcomes many of the shortcomings of the Snellen chart.[159]

2. Visual Acuity and Age-related Maculopathy

Distance VA may not be an effective test to quantify the functional deficit in patients with early ARM. According to Klein et al, each of the early ARM lesions in any subfield within the macular grid (hard/soft drusen plus pigmentary changes [increased retinal pigment or RPE degeneration] or soft indistinct drusen) is associated with a decrease in distance VA of approximately two or fewer letters when compared to eyes without such lesions.[169] Although this observation was statistically significant, such a level of visual deficit is neither clinically meaningful nor reliably detectable, given that the test–retest variability of logMAR chart is between one and two lines. Therefore, there is a consensus that distance VA cannot be used to determine or detect the presence of early ARM.

In contrast, GA and CNV, the two advanced forms of ARM, have a significant impact on VA. Klein et al, in a population-based study, reported that advanced ARM was associated with a significant decrease of approximately eight and six lines of letters read correctly in the presence or absence of central cataract, respectively.[169] Such a decrease in acuity was seen only when signs of advanced ARM involved the central area or inner subfields of the macular grid used in that study. Furthermore, locations of the missed letters provide approximate identification of the presence and position of the scotoma.

Geographic atrophy of the RPE progresses gradually over time, sparing the foveal center until the late stage of disease, and is associated with slow and gradual deterioration in VA. However, VA is a poor indicator of GA severity, because neither the extent of atrophic area, nor the degree of functional deficit, is directly related to VA. Sarks et al, in 208 patients with GA, demonstrated a wide range of VA with similar areas of atrophy, and this observation may possibly be due to a variable degree of retinal damage at the fixation point.[270] Furthermore, it was noted that the percentage of the fovea involved within the atrophic area was the most important parameter predictive of VA and that there was a progressive deterioration in VA with increasing percentage of foveal involvement, although this relationship was not linear. Similarly, Sunness et al investigated visual function in 74 eyes with GA, where VA was better than or equal to 20/50 and demonstrated a decrease in visual function (such as foveal dark adapted sensitivity and contrast sensitivity) in these eyes in spite of good VA.[307]

There is a high degree of agreement in the measured area of GA between fellow eyes, but a significant discrepancy in VA is observed between the better and worse seeing eyes. According to Sunness et al, this discrepancy in VA between the two eyes may either be related to the differences in the percentage of the fovea spared, or may possibly result from the suboptimal use of the worse-seeing eye.[303] Optimal ability to use the paracentral retina in the presence of a central scotoma may be reduced in the worse-seeing eyes of patients with bilateral advanced GA.

Furthermore, Maguire et al, in a small retrospective study of 14 GA eyes with good baseline VA, observed that five eyes demonstrating relatively rapid loss of VA over 19 to 34 months (average = 25.2 months) were associated with morphological changes characterized by increased encircling of the fovea by atrophy, coarse foveal granularity, thinning or attenuation of the

foveal RPE, and minimal drusen.[207] Similarly, Sunness et al demonstrated other risk factors for rapid deterioration of VA in patients with GA, in particular, functional presence of a dense scotoma including one-third or more of the parafoveal points tested within one degree of fixation, poor dark-adapted function at initial assessment, and encroachment of the foveal avascular zone by the atrophic area.[303]

Choroidal neovascularization, which may be subclassified into extrafoveal, juxtafoveal, and subfoveal, is associated with sudden and profound loss of vision. Of the three types of CNV, the subfoveal CNV that encroaches upon the foveal zone has the most deleterious impact on VA. However, and similar to GA, a wide range of VA may be observed in the presence of similarly sized lesions. Indeed, the Macular Photocoagulation Study of subfoveal CNV reported a wide range of VA using logMAR charts for each category of lesion size (small lesion: VA $\leq$ 1.0 = 21 eyes, VA 0.7–1.0 = 34 eyes, VA $\geq$ 0.70 = 48 eyes; medium lesion: VA $\leq$ 1.0 = 48 eyes, VA 0.7–1.0 = 48 eyes, VA $\geq$ 0.70=49 eyes; large lesion: VA $\leq$ 1.0 = 62 eyes, VA 0.7–1.0 = 34 eyes, VA $\geq$ 0.70=28 eyes).[206] This suggests that factors beyond the size of the lesion determine VA in patients with subfoveal CNV.

Furthermore, Doris et al examined the relationship between VA and other characteristics of macular lesions in 93 patients with subfoveal CNV due to ARM, and demonstrated that the greater the eccentricity at which the healthy retina begins and the greater the classic component of the lesion, the poorer the prognosis for VA.[96] In addition, these investigators observed that the impact of the macular lesion on VA depended on whether the study eye was the better-seeing eye or the worse-seeing eye. For example, a stronger correlation was reported between the severity of the macular lesion and visual function in the worse-seeing eye when compared with the better-seeing eye. An interplay of the psychophysical factors, such as retinal reserve and perceptual filling-in, may account for such a finding, and an eye may never reach its full potential unless forced to as a consequence of visual loss in the fellow eye.

Similarly, Hogg et al identified several components of CNV, in particular subretinal scarring, atrophy, blood, and exudates, which may influence VA in patients with CNV.[145] For example, subretinal fibrosis is associated with worse VA when compared with eyes that did not exhibit such scarring, possibly reflecting severe pathological changes in the normal architecture of the retina, consistent with the findings of Bressler et al.[44]

It is evident that there is inconsistency between the severity of morphological changes in advanced ARM and VA. The reason is that the photoreceptor mosaic is at the front end of the neural visual system, and processing of visual information starts with the sampling of the retinal image by this mosaic. Death or dysfunction of photoreceptors in ARM causes structural changes in the mosaic, such as reduced density and/or increased irregularity of the mosaic. Furthermore, VA is limited by the density of cone photoreceptor mosaic (or the spacing between adjacent cones), and this can be explained with the help of sampling theorem and Nyquist frequency. The sampling theorem states that a signal that is sampled at regular intervals can be reconstructed from its samples without loss of information if the original signal has no frequencies above ½ the sampling frequency. This critical frequency is commonly referred to as the *Nyquist limit* of the sampling array.[352] And, therefore, to decrease VA by one-half (i.e., to reduce spacing by 50%), the sampling density must be reduced by approximately 75%. In other words, a majority of the photoreceptors in the fovea must become dysfunctional or die before significant loss of VA is evident in ARM.[121]

a. Visual Acuity, Luminance, and ARM

The healthy eye is capable of responding to illuminated targets over a wide range of intensities, with a range greater than 10 log units.[178] According to Brown et al, increasing the luminance of the VA chart is associated with a parallel increase in VA; however, this increase in VA is greater in healthy subjects when compared with ARM patients at all the tested levels of luminance.[52] Conversely, Sunness et al investigated the best corrected VA in 74 eyes with GA and 13 eyes with drusen under conditions of decreased luminance.[307] A neutral density filter, which causes a reduction of 1.5 log units in luminance, was placed in front of the eye tested and the patient was requested to read a logMAR chart as far as possible. The eyes with GA exhibited a relatively greater loss in lines read when compared with drusen eyes under conditions of decreased luminance (GA: 4.6 lines; drusen: 2.2 lines), demonstrating that visual function under conditions of low luminance is adversely affected in eyes with GA when compared with eyes having early ARM.

b. Visual Acuity, Quality of Life, and ARM

Visual loss in patients with advanced ARM may affect many activities of daily life, several of which depend on both VA and CS. Low VA interferes with patients' ability to care for themselves and others, therefore, leading to incapacity and disability, and requiring the need for community and vision-related support.[298] Also, a reduction in VA is related to difficulty with close vision activities requiring fine resolution, such as reading small print in newspa-

pers, telephone directories, and medicine containers.[26] Furthermore, vision loss from advanced ARM has been observed to be associated with depression, which is similar to that of people with other chronic diseases.[259,354] However, VA is a poor predictor of vision-related activities, such as mobility, orientation, and face recognition.[261]

In conclusion, visual acuity, the standard test of visual function in the clinical setting, is not capable of quantifying functional deficits in early ARM. Furthermore, advanced ARM is associated with severe loss of VA; however, the degree of deterioration in VA may not parallel the severity of morphological changes at the macula. Lastly, VA is a poor predictor of vision related quality of life, such as face recognition and mobility, in patients with advanced ARM. Nevertheless, and in spite of these limitations, VA measured under standardized conditions using the logMAR charts remains the most commonly used primary outcome measure in clinical trials relating to ARM.

B. LOW-CONTRAST VISUAL ACUITY

Low contrast visual acuity, which is related to contrast sensitivity with a correlation range of 0.3 to 0.5,[240,252] is assessed using low contrast or variable contrast letter charts. These charts have a similar design to conventional acuity charts, with letters decreasing in size down the chart, although the letters are presented at relatively low contrast (<85% contrast) (Fig. 2). Some commonly used low-contrast visual acuity (LCVA) charts with good test–retest variability include the Regan charts,[252,253] the Bailey-Lovie chart,[21] and the Smith-Kettlewell Institute Low Luminance (SKILL) card.[134]

Four studies investigated LCVA in patients with ARM, and the data from all these studies suggest that there is a reduction in LCVA in ARM. Kleiner et al investigated LCVA using Regan letter charts in 52 patients with drusen, and demonstrated a significant decrease in LCVA in ARM patients when compared with age-matched controls, and this reduction was magnified as the contrast of the chart was further lowered to 9% and 3%.[170] Furthermore, patients with ARM demonstrated a significant trend of decreasing number of letters read correctly with increasing severity of the drusen. Similarly, Lovie Kitchin, Abadi et al, and Cheng et al in three different studies observed that LCVA is reduced in patients with ARM.[2,64,203]

C. HYPERACUITY

Hyperacuity measures the ability to discern misalignment of objects at the fovea, and is approximately 10-fold higher than VA.[146] The tasks used to measure hyperacuity include the detection of an offset between two lines, recognizing whether the line is curved or straight, and discriminating deviations from parallel.[151] Hyperacuity is relatively robust to optical blur and age-related decline and has been suggested to represent a better discriminator of early deficit in visual function in patients with ARM.[177]

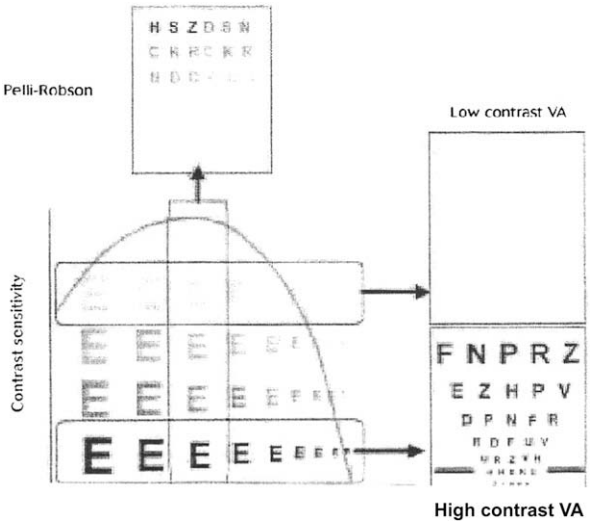

Fig. 2. Contrast sensitivity function and its relationship with visual acuity and low contrast visual acuity.

The recently developed shape discrimination (SD) chart consists of radial frequency (RF) patterns as test targets, and requires the patient to identify a deformed pattern from a cluster of perfect circles to assess hyperacuity.[337] SD involves integration across a wide retinal region, and, therefore, is more sensitive than conventional VA to irregular sampling or under sampling caused by photoreceptor dysfunction or death in patients with ARM.

Although it has been proposed that the extrastriate cortex may be responsible for processing SD,[355] this higher level mechanism needs uncontaminated information from the lower levels of the visual system to ensure optimal computation. In patients with ARM, if parts of an RF pattern fall on a healthy region of the macula and the other parts on defective areas, the information rendered to the higher-levels about the pattern is no longer optimal, and hence the threshold for detecting radial deformation may be elevated.

Indeed, Wang et al investigated hyperacuity using SD charts in 20 patients with early ARM and age-matched controls, and observed that patients with early ARM have significant deficits in performing SD tasks when compared with controls, in spite of good VA and CS.[337] Furthermore, patients with extrafoveal GA exhibited greater deficits on SD tasks when compared with patients having drusen and

pigmentary abnormalities, whereas VA failed to discriminate between these two classes of ARM. These results suggest SD tasks reflect the integrity of the photoreceptor mosaic in ARM.

D. READING SPEED

1. Definition and Basic Principle

Word reading is a complex task that can be described as a language code picked up through the visual system with further processing at higher levels,[183] and encompasses a variety of component processes, such as letter and word resolution, reasonably stable retinal images,[36,198,227] saccadic accuracy,[232] word encoding,[311] lexical accessing,[161] and cognitive processes required for comprehension and memory storage.[315] Word reading has been used extensively in psychophysical studies of visual function in patients with macular disease, and has been suggested a better discriminator of early deficits in visual function in patients with ARM.

Word reading speed depends on visual factors, non-visual factors, and stimulus conditions.[186–188,190–193,260,348] However, it is minimally affected by media opacities (such as cataract),[108,192] and is strongly associated with vision-related quality of life.[142] Furthermore, reading speed cannot be determined accurately in illiterate patients, and it is difficult to differentiate poor reading speed attributable to neural diseases versus cognitive defects.[107]

Currently, several reading assessment tests are available to evaluate reading function in low-vision patients, such as the Sloan Reading Cards, the William Feinbloom Sub-Normal Vision Reading Card, and the Woodcock Reading Test.[22] A drawback of these tests is that a subject may mask, to some extent, visual disability by guessing correctly on the basis of context, because cognitive comprehension processes can compensate for visual deficit in normally sighted individuals.[244,324] However, the Pepper Visual Skills for Reading Tests uses a sequence of unrelated letters and words that results in the absence of syntactic and semantic clues, and therefore forces individuals to rely exclusively on the visual information they can gather from the printed page to recognize the presented letters and words.

In subjects with normal vision, the average reading speed using central vision is 215 words per minute (wpm) with a range of 169–273 wpm.[188] With the normal aging process, there is a slight reduction in the reading speed (to about 70% of the young rate) for very small and very large characters; however, no significant difference is demonstrated over a range of character sizes for which normal reading was maximum.[3]

2. Reading Speed and ARM

As the corollary to the loss of central vision in ARM patients is a reduction in word reading speed,[115,189,192,262,302] and according to Mangione et al, 70% of patients with ARM expressed difficulty in reading "ordinary print."[208] The reasons for the reading deficit in patients with ARM are multifactorial, and include the need to use eccentric viewing, shrinking visual span, reduction in fixation stability, and impairment of eye movement control associated with the presence of central scotoma.

In ARM patients, reading is possible if they are able to consistently image successive words of text onto the usable eccentric retinal locations peripheral to the central scotoma; however, eccentricity by itself is considered to be an impediment to word reading speed. Various investigators have consistently demonstrated that reading performance, measured in terms of accuracy or latency, decreases as the stimulus is moved to positions increasingly further from the foveal center.[22,112,182,251] Similarly, Whittaker et al in a review article observed that reading speed decreases with increasing eccentricity of the retina, when VA, visual span, and precise measure of the scotoma size are taken into consideration.[348] In addition, based on two retrospective studies, these investigators demonstrated that the upper performance limit, which was estimated visually on the basis of the highest recorded reading performance in ARM patients, decreased linearly with increasing eccentricity of the retina.[80,81]

Furthermore, according to the "shrinking visual span" hypothesis, proposed by Legge et al, the number of letters recognized with each glance shrinks in peripheral vision when compared with central vision (center: 10 letters; 15 degrees eccentricity: 1.7 letters).[185] The reduced visual span in the peripheral vision allows fewer letters to be recognized in a single glance, and requires multiple fixation to recognize letters, whose length might exceed the size of the visual span.[184] Consequently, there is a reduction in word reading speed of ARM patients who use peripheral retinal loci for reading.

Poor oculomotor control, in terms of a decrease in the fixation stability, is frequently observed in patients with ARM, and it has been recognized as another important cause for poor reading speed. Crossland et al, in a small longitudinal study, demonstrated that ARM patients with poor fixation stability have slower reading speed than those with good fixation stability.[78] Furthermore, an increase in the fixation stability over a 12-month period after losing central vision accounted for 54% of the improvement in reading speed, thus suggesting that deficit in reading speed may be

attributable, at least in part, to impairment in fixation stability.

Furthermore, abnormal eye movements have been described in patients with ARM, and may contribute to poor reading speed. During reading, patients with ARM take longer to initiate saccades to the required target,[344,347] traverse fewer letters per forward saccade,[54,218] and have poor saccadic accuracy along with increase saccadic frequency. Frequent small saccades may slow reading rates due to the fact that small saccades have longer latencies, and require prolonged fixation between saccades.[173] Also, ARM patients with macular scotomata frequently need corrective eye movements during reading, and hypometric/hypermetric saccades and nystagmoid eye movements are commonly observed.[81,316,318,346]

It is important to note that not all the components of the reading process limit the reading performance in ARM patients because these individuals were typically proficient readers prior to the loss of central vision. Therefore, any subsequent reading disability in ARM patients can be reasonably attributed to the disruption in the ability for visual processing.

a. Reading Speed, Illumination, and ARM

There is a general consensus that the majority of low-vision subjects demonstrate an improvement in VA with increasing illumination,[74,160,195,285] and a similar effect is observed for reading speed. According to Bowers et al, the reading speed increased in ARM patients by 36 wpm (improvement by a factor of 1.4) when illumination level increased from 50 to 1,000 lux; however, no real increase in reading speed was observed with luminance levels above 1,000 lux.[37] It is believed that all subjects with ARM demonstrate some decrease in the scotoma area (size or shape) with increasing level of luminance, and consequently enhanced reading speed. In addition, Bullimore et al, observed that the saccade length (letters per forward saccade) increases with higher levels of illumination, and this increase in visual span may be attributable to a decrease in the scotoma area.[54]

Furthermore, few ARM patients benefit markedly from high levels of illumination (>5,000 lux), and patients who do exhibit this improvement often have active neovascular AMD, rather than GA.[286] It is believed that such improvement may be due to a dramatic change in the configuration of the scotoma area, and the development of an island of foveal vision. Alternatively, significant improvement in reading speed with increasing level of illumination in ARM may be because ARM patients use two different retinal loci for the fixation at low and high levels of illumination.[194]

b. Reading Speed, Preferred Retinal Locus and Cortical Adaptation, and ARM

The end-stage of ARM (GA and/or macular disciform scar) is characterized by the presence of a central scotoma, which results in the absence of retinal inputs from the fovea to the corresponding regions of retinotopically mapped visual cortex.[65] Consequently, these patients often develop adaptive strategies, such as preferred retinal locus (PRL),[116,132,330,344,346] possibly due to the reorganization of the visual cortex. According to Fletcher et al, 84% of 1,339 eyes with macular scotoma had an established PRL.[116]

The preferred retinal locus, defined as a discrete area of peripheral retina that contains the center of a target image for greater than 20% of a fixation interval,[346] develops in the presence of a dysfunctional fovea. The development of PRL may take up to 6 months, and takes place in the absence of explicit training or instruction. Furthermore, a sizeable proportion of patients may develop more than one PRL for a given task,[99,194,274,346] and this is frequently observed in patients with a scotoma involving greater than 20 degrees of the central visual field.[346] In addition, the fixation stability of the PRL, which is substantially less than in cases of normal fixation, is positively related to the duration of the disease process[344] but inversely related to the size of the scotoma.[346]

It has been postulated that those individuals with a pattern of frequent regression re-fixations (backward saccades) may use more than a single PRL for fixation, whereas those with multiple undershooting characteristics may use one PRL most of the time. Patients with multiple PRLs may use one PRL to identify small objects, such as bus numbers, and another PRL for identifying larger and more peripherally located objects.[230] Furthermore, according to Lei et al, some patients with ARM use a parafoveal PRL for fixation at low illumination levels, whereas a PRL located at or close to the fovea is used for fixation at high levels of illumination.[194] It appears that partially affected cones at a PRL for high illumination are able to function when given sufficient illumination.

Although the retinal location for development of a PRL is unpredictable, patients with ARM typically develop a PRL to the left of the retinal lesion, corresponding to an area to the left of the scotoma, even though this location is considered unfavorable for the reading task.[77,116,132,230,302] One possible explanation for this may be that this

location of a PRL seems optimal for mobility, face recognition, and watching television.[77] Alternatively, left-to-right reading, which is the most common way of reading English, may result in a higher prevalence of PRL to the left of the scotoma.[230] However, reading speed improves dramatically if a newly trained retinal locus is established in an area that is more favorable for reading (e.g., above or below the retinal lesion, sometimes as far out as 12 degrees of eccentricity).[230] This suggests that rehabilitation of ARM patients with an absolute central scotoma may be enhanced with appropriate training.

Various hypotheses have been put forward to explain the location of a PRL following the development of a central scotoma, and these may be classed as function-driven, performance-driven and retinotopy-driven.[65] The high frequency of a PRL to the left of the central scotoma, and a skewed distribution of the location of PRLs (with high frequencies of left- and lower-field PRLs), argues against the function- and performance- driven hypotheses for the spontaneous localizations of PRLs, respectively. The retinotopy-driven hypothesis relates to the adaptation of cortical mechanisms, and suggests spontaneous re-mapping of deafferented primary visual cortex neurons from retinal locations near the scotoma. The proximity of the PRL location and the scotoma borders, as demonstrated by various investigators,[116,302] seem consistent with this hypothesis; however, the high prevalence of left-field PRL is still not explained by such a hypothesis.

It is important to note that macular scotometry, based on conventional perimetry, has limited validity in advanced AMD patients with a PRL[210,341] because conventional perimetry assumes stable foveal fixation, which is a false assumption in AMD patients with a PRL. Therefore, microperimetry may prove to be an invaluable technique for assessing and monitoring the scotomata in ARM patients with a PRL.[308,316,317,339] It is important to note that microperimetry using SLO is no longer available, but the equivalent microperimetry can be performed using the Nidek Microperimeter 1,[223] which is increasingly becoming a technique of choice for assessing visual sensitivity in patients with unsteady fixation and eccentric PRL.

c. Reading Speed, Rehabilitation, and ARM

Word reading is the single most important rehabilitative goal of ARM patients with low vision, and nearly two of three patients with low vision want to regain the ability to read.[336] Currently, several techniques exist that can enhance the reading performance of patients with ARM, such as optical or electronic magnifying devices, eccentric viewing training, contrast enhancement, and use of other non-optical methods, such as supplementary lighting.[37]

Recent studies have demonstrated training-related improvement in peripheral reading performance;[229,230] however, a small subgroup of patients do not achieve acceptable reading speed despite extensive rehabilitation, and it is important to identify such patients before starting rehabilitation. McMahon et al assessed reading speed in 13 patients with AMD before and after an intense vision rehabilitation program over a 6-week period.[217] The results suggested that patients with reading speed less than 10 wpm, greater than two errors for a short passage, and saccadic frequency score of greater than 2, are less likely to show improvement in reading speed with vision rehabilitation when compared with patients who do not exhibit such limitations.

Furthermore, Crossland et al, in a longitudinal study, investigated a variety of demographic and clinical measures to assess their predictive value in determining patients' future reading speed, and demonstrated that contrast sensitivity can predict the likelihood of future fluent reading in ARM patients.[79] However, baseline reading speed, VA, age, disease type, and scotoma size were poor predictors of future reading performance.

In conclusion, ARM patients with macular scotoma demonstrate a reduction in reading speed. Furthermore, reading speed may improve if a new PRL is established in an area that is more favourable for reading (i.e., above or below the retinal lesion); however, training by a skilled low vision therapist is essential for success.

E. CONTRAST SENSITIVITY

1. Definition and Basic Principle

The term *contrast* is a physical dimension, which refers to light–dark transition of a border (or an edge) in an image that delineates the existence of a pattern or an object.[236] The amount of contrast required by an individual to visualize a target is known as *contrast threshold*, and clinically, contrast threshold is expressed as CS, where sensitivity is the reciprocal of threshold.

The contrast in relation to periodic pattern (Michelson contrast), such as sine-wave grating, refers to the luminance of the maximum brightest area minus the luminance of the minimally dimmest area, divided by their sum.[91,343] The contrast in terms of non-periodic pattern (Weber contrast) is defined as the difference between maximum and minimum luminances, divided by the minimum luminance.[1]

The CS function refers to a curve where CS is plotted as a function of spatial frequency (SF) on

log–log coordinates, and represents the minimum contrast required for detection of sine-wave (SW) gratings of various SF (Fig. 2). In normal subjects, under photopic conditions, CS function peaks at intermediate SFs (3–6 c/d) with a steep roll-off at high SFs and a gradual roll-off at lower SFs,[236] the limiting factors being optical (diffraction and aberrations) and neural (spatial summation by neural receptive field), respectively.[13,72] It is believed that the human visual system possesses multiple neural spatial frequency filters, each with specific spatial-tuning characteristics, and this unique configuration of the filters may contribute to the physiological basis for CS function.[32,59,60,266,277]

Acuity in terms of CS function is defined as the highest SF that can be detected at 100% contrast, and is a measure of the resolving power of the visual system.[236] In normal subjects with foveal fixation, there is a good degree of agreement between grating and Snellen acuity. A CS plot where CS function is compared between pathologic states and the population norm is known as a *visuogram*, a term introduced by Bodis-Wollner.[34] A visuogram near the zero level implies a normal CS function, and points below zero indicate the amount of CS deficits, in decibels.

The most common way of measuring CS in clinical research is by varying the contrast of SW gratings, which consist of striped patterns matched with uniformly gray targets of similar luminance. Although these tests measure CS over a range of SFs, they are relatively expensive and time consuming, and, therefore, unsuitable for clinical practice.[359] Letter-optotype charts, such as the Pelli-Robson chart, represent an alternative and common way of measuring CS in clinical studies. The test optotype is familiar to both patients and investigators, and consequently these charts are easy to present, unlike grating charts. Also, CS measured by these charts is moderately associated with VA, the correlation coefficient being approximately 0.5 to 0.6.[174,256,263] Furthermore, the CS assessed on these charts is highly predictive of reading performance.[345] Finally, CS function in various pathological conditions can be compared with available normative data.[109]

Contrast sensitivity function reduces with age for medium and high SFs, with a shift of peak towards low SF, and this is noted over a wide range of luminances.[75] Indeed, Burton et al have observed that individuals above 70 years (yrs) of age require approximately 3-fold greater contrast to detect a target when compared with young adults in their second decade.[55] The confounding effect of age on CS function should be taken into account when investigating visual function in patients with ARM.

2. Contrast Sensitivity and ARM

Eleven studies that have investigated CS function in patients with ARM are summarized in Table 1.[50,53,114,150,170,202,219,221,283,294,358] The data suggest that there is loss of CS across all SF in patients with ARM, with significant reduction at medium and a high SF. Furthermore, CS function is relatively preserved at low SF in the early stages of disease. A plausible mechanism underlying loss of CS function in ARM may reflect decreased efficiency of the lateral inhibitory mechanisms that are mediated by horizontal and amacrine cells.[50,52]

Three studies have examined whether CS function varies with respect to disease severity, measured in terms of drusen (type, number, confluence), pigment alteration, and GA, and two have found a significant association.[170,221,294] Midena et al observed loss of CS at high SFs with drusen confluence (but not with drusen number), focal hyperpigmentation of the RPE, and atrophy of the RPE.[221] Similarly, Kleiner et al demonstrated a significant loss of CS at high SF, along with a reduction of peak CS with increasing severity of drusen.[170] However, in that study, drusen number, size, and degree of confluence were bracketed into a single drusen grade, and therefore correlation of an individual drusen characteristic with CS function was not possible. These observations suggest that worsening of CS function may reflect disease progression in terms of morphological changes.

Furthermore, Midena and co-investigators also attempted to identify a link between CS function and the risk for progression to neovascular AMD.[221] For this purpose, CS function was compared between fellow eyes of patients with unilateral neovascular AMD and eyes with bilateral early ARM; however, no significant difference in CS function was observed between the two groups. Similarly, Stangos et al failed to demonstrate a significant difference in CS function in 17 eyes with bilateral drusen when compared with 14 fellow eyes of patients with unilateral neovascular AMD.[294] The data from both of these studies imply that reduction in CS, and the measure of CS, is not of prognostic value for the subsequent development of neovascular AMD.

Brown et al investigated CS as a function of eccentricity in eight patients with ARM and age-matched controls.[53] CS was measured using SW gratings at eccentricities of 0°, 2°, 5°, and 10°, the order of testing at various eccentricities being random. The CS in ARM patients was depressed at the fovea and at all tested eccentricities when compared with healthy subjects; however, the difference between ARM and controls at all eccen-

TABLE 1

Studies Which Have Investigated Spatial Contrast Sensitivity in Patients with Age-related Maculopathy

Principal Investigator/Year of Publication	Types of Study	Sample Size	Age in Yrs Mean/ range	ARM Status and Visual Acuity	Nature of Stimulus	Conclusion
Sjostrand et al (1977)[283]	Case-control	Cases-3 Controls-10	64–78	AMD VA-0.7 t0.8	Sinusoidal grating	Pts with AMD have marked loss of CS at intermediate and high SF.
Wolkstein et al (1980)[358]	Cross-sectional	4 pts	*	AMD VA-20/40 to 20/400	Sinusoidal grating	Pts with AMD have CS loss at high SF.
Hyvarinen et al (1983)[150]	Cross-sectional	2 pts	*	Study eye-CNV VA 0.05 to 0.1	Sinusoidal grating	Pts with ARM have CS loss at all SF using small grating field, but marked loss at high SF with a large grating field.
Brown et al (1983)[50]	Case-control	Cases-6	72.4 (64–85)	Study eye-pig changes, 2 pts; drusen plus pig changes, 2pts CNV 2 pts	Sinusoidal grating	Pts with ARM demonstrate loss of CS at high luminance levels along with shifting of peak to lower SF. However, no loss of CS at scotopic levels
		Controls-5	70.6 (67–74)	VA-cases; 6/9 to 6/18; controls; 6/6		
Loshin et al (1984)[202]	Cross-sectional	40 pts	>70	Study eye GA or CNV VA-20/26 to 20/560 CS assessed in both eyes	Sinusoidal grating	Pts with ARM demonstrated CS loss et al SF, and the peak CS was reduced and shifted towards lower SFs. The preferred eye of pts appeared to be related to peak CS rather than VA
Brown et al (1987)[53]	Case-Control	Cases-8	69.8 (63–82)	Study eye-drusens and/or pigmentary changes	Sinusoidal grating	Pts with ARM have reduced CS function centrally as well as paracentrally up to 10 degrees ecentricity
		Controls-8	71.3 (66–77)	VA-6/7.5 to 6/19; control:6/6		
Kleiner et al (1988)[170]	Case-control	Cases-21 Controls-7	41–75 55–75	Study eye-Drusen, graded from 1 to 4 Gr 1-few, discrete & Gr 4-numerous, large and confluent drusen VA 20/20	Ginsberg chart	Pts with ARM have decrease in CS at high SF as well as a decrease in peak CS with increasing drusen grade
Strangos et al (1995)[294]	Case-Control	Cases-23	66.04 (38–76)	Study eye-BE drusens: 9 pts; drusen in fellow eyes of pts with UL AMD: 14 pts	Sinusoial grating	Pts with ARM have CS loss at all SF; however, it is statistically significant only at middle and high SF. There was no difference in CS among different drusen subgroups or between eyes with BL drusen and fellow eye of pts with UL AMD
		Controls-32		VA-10/10		
Midena et al (1997)[221]	Case-Control	Cases-47	65.30 (51–74)	Study eye -BE ARM: 34 pts fellow eye of pts with UL AMD: 13pts. Early ARM was defined by the presence of soft drusen ≥63 μm and/or pig change and/or RPE atrophy.	Sinusoial grating	Pts with ARM have significant decrease in CS at all SF when compared with controls. The presence of focal hyperpig and RPE atrophy was associated with significantly lower CS at SF of 20 cycles/degree. No statistically significant difference of CS was found between eyes with BL ARM and the fellow eyes of patients with UL AMD.
		Controls-36	64.33 (51.75)	VA ≥ 20/25		

Feigl et al (2005)[114]	Case-control	Cases-13	63–77	Study eye-early ARM, defined as hard or soft distinct and indistinct drusen ≥ 63 μm with or without RPE changes	Pelli-Robson chart	Pts with ARM have significantly impaired CS.
		Controls-13		VA-6/6 to 6/12		
Mei et al (2007)[219]	Case-control	Cases-27	81	Study eye-GA: 13 pts; CNV: 14 pts	Sinusoidal grading	Pts with ARM have decrease in CS at all SFs along with shifting of peak to lower SF, and this deficit in CS increased with increasing SF.
		Controls-15	70	VA-GA: 0.8; CNV: 1.0		

*Not available. AMD: Age-related macular degeneration, ARM: Age-related maculopathy; BE: Both eyes; CNV: Choroidal neovascularization; CS: Contrast sensitivity; GA: Geographic atrophy; Gr: Grade; Pt(s): Patient(s); RPE: Retinal pigment epithelium; SF: Spatial frequency; UL: Unilateral eye; VA: Visual acuity.

tric locations failed to reach statistical significance. This finding strengthens the evidence that CS, along with other psychophysical functions, is disrupted and compromised at retinal locations remote from the fovea, suggesting that ARM is not confined to the fovea and parafoveal regions.

Many patients with ARM complain of visual disabilities associated with changing levels of luminance. This prompted Brown and co-investigators to examine the effect of luminance on CS function in patients with ARM and in age-matched normal subjects.[50] Patients with ARM demonstrated a loss of CS function at photopic and mesopic luminances, with relative preservation at scotopic luminances, along with shifting of the peak function to low SFs at all luminances. These results suggest that adaptation mechanisms, which allow optimum functioning of the visual system over a wide range of luminances, are compromised in the disease process of ARM.

A reduction in CS function often parallels loss of VA; however, a considerable dissociation between these two measures of visual function occurs in patients with ARM. Patients with advanced ARM may have greatly reduced VA with near normal CS at low SFs, and reasonably good CS at middle SFs, and vice versa. This concept of "hidden vision" was first proposed by Hyvarinen et al in 1983.[150]

A loss of CS function in patients with ARM will greatly influence vision-related quality of life, by various mechanisms.[76,224] First, loss of CS will impair a wide range of activities for daily living such as eating, dressing, pouring drinks, and using kitchen utensils. Second, CS is closely related to reading performance, and a slow reading speed may alter the understanding of print, such as a price tag or the address on an envelope. Third, CS is vital for the task of face and object recognition, and is the single most important aspect of visual function in determining the accuracy of identifying an icon on a computer monitor.[275] Fourth, loss of CS at middle and low SF has important consequences for orientation and mobility. According to Cummings et al, a decrease in CS was significantly associated with an increases risk of hip fracture in a subgroup of 10,000 women over the age of 65.[82] Finally, CS is associated with self-reported difficulty in certain driving tasks, in particular difficulty on left turns, parallel parking, and driving on high traffic roads.[76]

In conclusion, patients with ARM have significant disruption of CS function at high and medium SFs, measurable at up to eight degrees of retinal eccentricity. Furthermore, a progressive loss of CS function may reflect disease progression; however, such a loss is unable to identify eyes at particularly high risk for developing neovascular AMD. Lastly, measurement of CS function may provide insight

into the extent of functional disability in ARM patients with no apparent loss of VA.

VII. Temporal Function

Temporal function represents the response of an eye to a flickering stimulus, and can also be assessed for non-periodic stimuli. For instance, temporal integration can be assessed by measuring the period of time over which response summation occurs, and temporal resolution can be assessed with two-pulse discrimination. In this context, temporal summation refers to the eye's ability to sum the effects of individual quanta of light over time, and it only occurs within a certain period of time (known as critical duration or critical period). Temporal function has been reported to be affected by various ophthalmic disorders,[47,131,327–329] and may be a particularly suitable parameter in elderly patients with ARM because flicker sensitivity is robust to both the spatial parameters of the stimulus and the refractive status of the patient.[175,212,326]

The two types of flickering stimuli, which are used for assessment of temporal function, include mean modulated flicker and pedestal flicker.[9] In *mean modulated flicker*, the stimulus is altered around a mean background level in such a way that there is no change in the time-averaged luminance. In contrast, the *pedestal flicker* involves modulating a stimulus concurrent with light increment, which results in an increase in the flickering component along with time-averaged luminance above background level. Classically, the opponent (chromatic) and the non-opponent (luminance) systems detect flicker for low and high alteration rates, respectively.[215]

A flickering light stimulus may detect functional changes in the retina of ARM patients earlier than static stimuli. The reason is that blood flow in the retina, similar to other neural tissues, is tightly coupled to the neural activity, and, therefore, an increase in the neural activity of the retina, induced by a flickering stimulus, requires a parallel increase in the blood flow of the retina.[168,331] In patients with ARM, thickened and lipid laden Bruch's membrane decreases the hydraulic conductivity and aqueous diffusion across the choroid, resulting in diminution of vascular endothelial growth factor secretion into the choroid, and consequential atrophy of the choriocapillaris.[16,356] As the outer retina (including photoreceptors) is dependent on the choroidal circulation for blood supply, increased retinal blood flow imposed by a flickering stimulus may not be readily met in patients with ARM.[245] In addition, Metelitsina et al demonstrated that choroidal blood flow is about 16.7% lower in ARM patients associated with systemic hypertension when compared with ARM patients without systemic hypertension.[220] This suggests that a reduction in the choroidal blood flow in ARM patients may actually be further reduced in subjects with a history of cardiovascular disease.

The human eye is capable of responding to flicker rates of up to 60–80 Hertz (Hz);[51] however, the cone responses are diminished at temporal frequencies above 10–15 Hz because of cone–cone interactions and/or neural filtering that is accomplished through a series of filtering stages, distributed across multiple retinal and cortical loci.[281] Furthermore, flicker frequencies of less than 25 Hz are detected by both the rod and cone photoreceptors,[4,143,284] but cone responses predominate at higher flicker frequencies, and indeed the rod responses at these frequencies are mediated via cone photoreceptors. It is believed that the magnocellular pathway is sensitive to higher temporal frequencies whereas the parvocellular pathway carries information at lower temporal frequencies.[276]

A. TEMPORAL RESOLUTION

When intermittent stimuli are presented to an eye, the stimuli appear to stay on, but with a change in intensity or motion (flicker). However, if the rate of presentation of intermittent stimuli exceeds a certain critical rate/frequency, then the perception of flicker ceases and is replaced with a sensation of steady light, and such a frequency is known as critical flicker frequency (Kolb et al 2002; http://webvision.med.utah.edu/). Critical flicker frequency (CFF), in other words, represents the highest resolvable flicker frequency, and is analogous to the resolution of spatial VA in the temporal domain, and provides less information on temporal function than does the full temporal contrast sensitivity curve.

Hammond et al investigated CFF in 134 healthy subjects ranging from 17 to 92 yrs, and demonstrated that subjects with the highest MP density have about 25% higher CFF values than subjects with the lowest MP density, suggesting that MP optical density may exert a protective effect on visual health across lifespan.[137] Indeed, L has been shown to improve gap-junction communication that may improve cell-to-cell communication within the neural tissues.[293]

However, Hammond et al's finding should be interpreted with full appreciation of the limitations of the study as follows: first, removal of the outliers from Fig. 2 in that article (all of which relate to the elderly subjects), will result in disappearance of the relationship observed by the investigators.

Second, because MP optical density was measured using a flicker technique (heterochromatic flicker photometry), an inherent confound exists.

Furthermore, Brown et al investigated CFF in patients with pre-ARM (early ARM in the presence of normal VA) and ARM, and observed that CFF is relatively reduced in patients with ARM when compared with pre ARM, and when compared with control groups.[51] In addition, the CFF values did not vary significantly at 0, 10, and 20 degrees of retinal eccentricity in ARM patients, suggesting that this temporal function does not vary as a function of eccentricity. However, CFF is higher in the peripheral visual field than in center, whether or not the size of the stimulus is scaled with eccentricity, in normal subjects.[97,249,250,258,342]

B. TEMPORAL CONTRAST SENSITIVITY

The temporal contrast sensitivity (TCS), also known as *de Lange function*,[90] measures the temporal frequency characteristics of the human eye by varying the modulation depth of a sinusoidal flicker, and can be analyzed in a manner similar to the measurement of contrast thresholds for a spatially modulated stimulus.

This psychophysical function is described as an envelope that represents the combined response profile of mechanisms (channels/filters) whose individual response spectra are overlapping; however, there is an uncertainty about the minimum number of mechanisms underlying TCS. At frequencies where one mechanism is more sensitive than others, its response dominates contrast detection, and discriminating one flicker rate from another may require differential activation of at least two mechanisms (low and high mechanisms). Furthermore, according to Mayer et al, parsimony favours the two-mechanism model but the patterns of loss associated with ARM are more easily understood in terms of three underlying mechanisms (low, medium, and high mechanisms).[211]

Brown et al investigated TCS function in ARM patients and age-matched controls, and demonstrated a significant decrease in temporal sensitivity across a wide range of frequencies, with predominant disruption at low and medium frequencies.[51] In addition, this disruption of temporal function was found to extend as far as 20 degrees from the fovea, and may be related to alterations in the photoreceptors, disruption of functional connections between receptors, or reduced cone function secondary to functional loss in the RPE cell layer.

Furthermore, Haegerstrom-Portnoy et al investigated two-color increment threshold in ARM patients and control subjects, and demonstrated that the ability to detect flicker at 25 Hz was significantly decreased in ARM patients when compared with elderly control subjects, despite these patients having normal L-cone increment threshold.[135] Similarly, Applegate et al observed a decrease in flicker sensitivity by 0.5 log units in early ARM patients with normal L-M-cone sensitivities.[12]

Mayer et al, in a series of studies, investigated temporal CS function in the fellow eyes of patients with unilateral CNV.[213–215] Similar to Brown et al, these investigators observed that foveal flicker sensitivity was depressed at low- to mid-temporal frequencies in patients with ARM when compared with controls.[214] Furthermore, in a subsequent study, the investigators demonstrated that foveal flicker sensitivity at two temporal frequencies, 14 and 10 Hz (in order of estimated weight), can distinguish a healthy eye from an eye at risk for developing CNV with 78% accuracy, using a stepwise discriminant analysis.[213] Lastly, in another study, the same investigators reported that modulating the flicker sensitivity at only two frequencies (5 and 10 Hz) might successfully identify a pre exudative eye from healthy eyes with 100% accuracy.[215]

Whether a loss of flicker sensitivity in ARM patients reflects receptoral or post-receptoral damage is still a matter of debate. Mayer et al believe that early ARM may affect photoreceptors, and selective losses in the flicker sensitivity observed in their studies suggest that dynamics of the photoreceptors' responses are affected at an early stage.[214] These dynamic changes may then later differentially affect some higher-level mechanisms, such as a luminance channel, more than others (e.g., a chromatic channel). However, Haegerstrom-Portnoy et al proposed that in ARM patients a post-receptoral channel for detecting a flickering stimulus might be involved.[135] These investigators believe that a change of 0.3 log units in M-cone sensitivity noted in their study, along with no significant change in L-cone sensitivity, would have produced only minor changes in the flicker sensitivity if the losses have occurred at the receptoral level.

In conclusion, the published data indicates impairment of temporal function in patients with ARM, and loss of foveal flicker sensitivities at two temporal frequencies may identify eyes at risk for developing neovascular AMD. However, it should be noted that there is a paucity of studies, which have investigated this psychophysical function in patients with ARM.

VIII. Visual Adaptation in Age-related Maculopathy

Visual adaptation refers to a remarkable ability of the human eye to function over a wide range of luminances (greater than 10 log units), and is

achieved through a coordinated action of mechanical, photochemical, and neural processes in the visual system.[178] The integrity of these visual processes can be assessed using psychophysical tests such as dark adaptation (DA) of rods and cones and the glare recovery test.

A. DARK ADAPTATION

1. Definition and Basic Principle

Dark adaptation, also known as *bleaching adaptation*, refers to the slow recovery of visual sensitivity in dark following exposure of an eye to light that bleaches a substantial portion of visual pigment in the photoreceptors.[178] In biochemical terms, this process includes recovery of visual threshold, resumption of circulating currents in the photoreceptors, and regeneration of photoreceptor pigment.

The classic DA curve is obtained after almost total bleach, and consists of two distinct regions of recovery (Fig. 3). The first phase of recovery is associated with 1.5–2 log units of increase in visual sensitivity (cone function: 8 minutes), and the second phase involves a visual sensitivity change in excess of 4 log units (rod function: 20–30 minutes). At the junction of these two phases lies a transition zone, known as *rod–cone break* (11 minutes), which represents a transition from cone to rod function. In other words, cone sensitivity is no longer greater than rod sensitivity, and it no longer continues to increase with time. It is important to note that the rod-mediated adaptation begins as soon as the light is extinguished; however, this is not evident in a normal DA curve because the initial phase of rod adaptation is obscured by the cone-mediated phase of recovery. Also, the magnitude of loss in visual sensitivity is not proportional to the amount of the visual pigment beached, which may vary from 0.5% to 98%. For instance, a bleach of just 20% of the visual pigment causes an elevation of visual threshold of more than 1,000-fold, and the visual threshold may remain elevated at this state even after a couple of minutes in darkness even though at least 80% of the unbleached pigment was present in the eye.

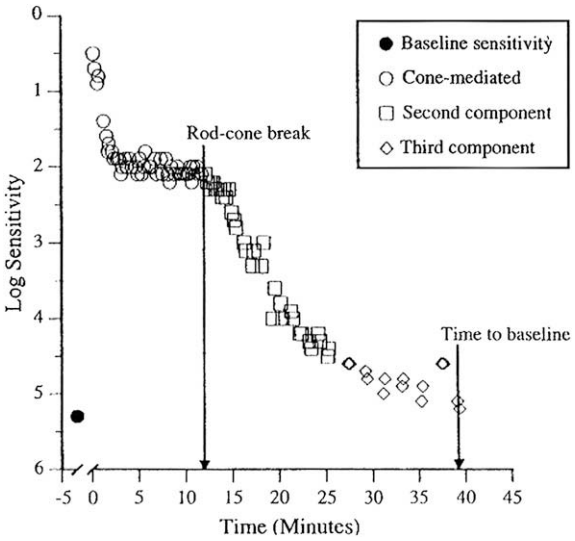

Fig. 3. The dark adaptation curve.

In some patients, following delivery of bleach, the DA rod threshold (scotopic threshold) may be within normal limits in the presence of a significant delay in the time course of DA. This indicates that there is no actual loss of rod photoreceptors, and that all rhodopsin is regenerated after a sufficiently long period of DA, thus suggesting that the mechanism underlying these two aspects of rod vision is not identical. Furthermore, some patients may be erroneously described as "night blind" because of extreme prolongation to regain full scotopic retinal sensitivity.[178]

With age, there is a progressive thickening of Bruch's membrane from the deposition of high levels of neutral lipids, which causes the membrane to become hydrophobic.[243] This structural change, by acting as a barrier, limits the availability of vitamin A to RPE and/or decreases the transport of 11-*cis*-retinal from RPE to the rod outer segment, thus delaying the regeneration of rhodopsin. Indeed, Jackson et al have demonstrated slowing of DA with aging in a group of 94 subjects, and when expressed in fractional terms, the rate of DA at age 90 years averaged 64% of its value at age 20 years.[154] Furthermore, there is a three-fold rise in the absolute scotopic threshold from age 20 to 90 years; approximately 0.07 log units rise per decade.

In this review article, we have sub-divided DA into steady- (scotopic and photopic retinal sensitivity) and kinetic-state function, and have adopted the following definitions. Scotopic retinal sensitivity is defined as the measurement of retinal sensitivity (RS) beyond the fovea using sufficiently short wavelength stimulus (wavelength range: 450–550 nm approx.) following 30–45 minutes of pre-adaptation in dark, and is presumed to be mediated exclusively by the rod photoreceptors. Photopic retinal sensitivity refers to the measurement of RS using long wavelength stimulus (wavelength: 600–650 nm approx.) presented on a steady white background to the fovea with 5–10 minutes of pre-adaptation to light, and is mediated by the cone photoreceptors.

Furthermore, by kinetic aspect of DA function, we refer to the recovery of RS to baseline (pre-bleach) level following exposure of an eye to intense illumination that bleaches a substantial level of

photopigment. It is possible that an additional pathway exists for regeneration of cone photopigment,[56,155] with an 11-*cis*-retinyl ester pool within the retina serving as a photopigment regeneration source;[322] however, the specific mechanism for the 11-*cis*-retinal production within the retina itself remains unclear.

2. Dark Adaptation and Age-related Maculopathy

Patients with ARM often complain of difficulty in performing various activities at night and under low levels of illumination, such as reading and driving, in spite of good VA. These deficits may vary with illumination, and are not attributable to intraocular light scattering as a result of corneal or lenticular opacities and/or pupillary abnormalities. Additionally, patients may complain of worsening of vision after several minutes in bright sunlight, slow recovery after exposure to bright light, and a central scotoma in the dark.[297] It is worth mentioning that certain systemic conditions, such as hepatic or biliary cirrhosis, chronic bowel disease, protein calorie malnutrition, and sickle cell anaemia, are known to cause abnormal DA, and the medical history should be directed toward the possibility of these conditions when a patient is complaining of difficulty with night vision.[100,144,228,265,338]

Indeed, histopathologic studies of human donor retinas suggest that there is a selective predilection for loss of rods over cones in early ARM.[85] Although both rods and cones degenerate in ARM, rod loss precedes cone loss in 75% of early and late ARM eyes. The maximum loss occurs in the parafovea, 1–3 mm from the fovea (3.5–10 degrees from fixation),[153] beginning inferior to the fovea and culminating in an annulus of deepest loss at 0.5 to 3 mm eccentricity.[86,153] It is important to note that the annulus lies closer to the foveal center than the elliptical ring of highest rod density (4–6 mm from the fovea), indicating that the loss is not spatially correlated with rod density.[86] However, in 25% of ARM eyes, cone loss predominates rod loss, and it has been hypothesized that such eyes may represent a distinct subtype of ARM.[153]

Twelve studies that have investigated DA function in patients with ARM are summarized in Table 2.[49,52,105,106,136,152,237,238,273,297,304,306] Eight studies examined scotopic retinal sensitivity in patients with ARM,[49,52,136,152,237,238,273,297] and all except two[136,152] demonstrated a reduction in scotopic RS. Furthermore, of the six studies evaluating the kinetic aspect of DA function,[105,106,136,152,238,297] five have consistently observed a prolongation in the time course for pigment regeneration in patients with ARM.[105,106,136,238,297] These psychophysical observations are thus consistent with the histopathologic findings of selective vulnerability for rod photoreceptors in patients with ARM.

Haimovici et al failed to observe a decline in the scotopic RS in 31 patients with ARM, and possible explanations for such an observation may be the absence of either symptoms or less advanced disease in that study population.[136] Similarly, in a recent study, Jackson et al failed to observe abnormalities in scotopic sensitivity and kinetic aspect of DA in 19 patients with early ARM when referenced against elderly subjects with healthy retina; however, in that study DA was assessed using Scotopic Sensitivity Tester-1 (SST-1, LKC Technologies, Gaithersburg, MD, USA).[152]

Two studies have evaluated scotopic RS in a region overlying drusen area, and compared it with that of a retinal area not involved by drusen. Sunness et al were unable to demonstrate a difference in scotopic RS over drusen when compared with a non-drusen region, regardless of the type or size of drusen or the status of the fellow eye.[304] However, a decrease in scotopic RS was observed in patients with confluent drusen associated with atrophic changes in the RPE. In contrast, Scholl et al demonstrated a decline in the scotopic RS in a single patient with a large soft druse present at the fovea, and because a druse represents a small RPE detachment, perhaps it was unsurprising to observe an associated decrease in scotopic RS in this patient.[273] This finding is consistent with that of Hamovici et al, in which a relatively greater degree of dysfunction in the kinetic aspect of DA was observed in 11 eyes with RPE detachment.[136]

Eyes with an RPE detachment exhibit a profound deficit in the kinetic aspect of DA function because the hydrophobic nature of Bruch's membrane, secondary to deposition of neutral lipids, impedes movement of ions and water into the choroidal circulation.[28,29,31,243] Consequently, there is an altered metabolic exchange between the choroid and the RPE, leading to accumulation of fluid in the sub-RPE space, and a subsequent delay in the time for regeneration of photopigment.[225,295,296] Other hypothesized mechanisms, which may play a role in the pathogenesis of kinetic aspect of DA abnormalities in RPE detachment, include intrinsic abnormalities of RPE cell number or function,[200] photoreceptor dysfunction, and cell death,[95,200] or a combination of these factors.

A study by Sunness et al investigated the absolute sensitivity at the fovea following DA in 18 patients with ARM using a Tubinger perimeter and a 1.8-degree red target.[306] All these patients were followed prospectively for a median of 45 months (range 42 to 50 months), at the end of which one eye developed CNV, three eyes developed RPE

TABLE 2

Studies Which Have Investigated Dark Adaptation Function in Patients with Age-related Maculopathy

Principal investigator/Year of Publication	Type of Study	Sample Size	Age in Yrs Mean/range	ARM Status and Visual Acuity	Name of Instrument *(DA function tested)*	Conclusion
Brown et al (1983)[52]	Case-control	Cases-8	74.5 (66–83)	Senile macular degeneration *	4 light emitting ldiodes in cross configuration *(Scotopic sensitivity)*	Significant loss of scotopic sensitivity in pts with ARM when compared with controls. 50% of the ARM pts have prolonged DA. Good degree of correlation between symptoms and findings.
		Controls-6	68 (63–74)	VA-cases: 20/60 to 20/400; controls: 20/20		
Brown et al (1986)[49]	Case-control	Cases-4	70.25 (67–74)	ARM-drusen and/or pig changes, 2pts AMD-CNV: 1 pt; GA: 1pt	Dark adaptatometer *(Scotopic & photopic sensitivity)*	Abnormalities in both rod and cone adaptation system. Marked increase in rod threshold particularly at the fovea, and up to 25 degrees ecentricity.
		Controls-5	65 (58–74)	VA-Cases: 20/25 to 20/40; Controls: 20/20		
Sunness et al (1988)[304]	Cross sectional	8 pts	55–86	Study eye-drusen and/or pig changes Fellow eye-CNV: 3; Drusen: 5 VA-20/16 to 20/40	Fundus Camera Stimulator *(Scotopic sensitivity)*	No significant difference in DA retinal sensitivity directly over drusen area when compared with non drusen area, regardless of type or size of drusen and status of fellow eye.
Sunness et al (1989)[306]	Prospective (median, 45 mo)	18 pts	57–81	Study eye-drusen, graded from 0 (no drusen > 125 μm) to 6 (large confluent drusen). Fellow eyes: drusen, 7 pts; PED, 3 pts; GA: 1 pt; CNV: 7 pts VA-20/16 to 20/50	Tubinger perimeter 1.8 degree red stimulus (Absolute DA foveal sensitivity)	Absolute foveal DA sensitivity is an excellent predictor of AMD development (100% sensitivity and 92% specificity), and performed better than initial visual acuity, drusen characteristics, and status of fellow eye.
Eisner et al (1991)[106]	Cross sectional	41 pts	≥60	Fellow eyes of patients with UL CNV (Drusen and/or hperpig and/or atrophy) VA ≥ 20/25	**(photopic sensitivity)*	High risk eyes (large drusen size, more than minimal drusen confluence and focal hyperpig) were associated with significant slower rate of recovery than low risk eyes.
Eisner et al (1992)[105]	Prospective (18 mo)	47 pts	55–86	Fellow eyes of patients with UL CNV (Drusen and/or hyperpig and/or atrophy) VA ≥ 20/25	**(photopic sensitivity)*	DA, in combination with colour matching, was the most effective combination of visual functions for distinguishing those eyes found to develop CNV at 18 months up.
Steinmeiz et al (1993)[297]	Case-control	Cases-12	76	Study eye-drusen (FFA-hypoflurosecent 75%; associated prolonged choroidal filling 50%)	HVF (modified for scotopic conditions) *(scotopic sensitivity)*	In 50% of the ARM pts, scotopic thresholds were depressed and associated with symptoms of central scotoma in the dark or poor night vision. DA was prolonged and there was no correlation between the quantity of drusen and nature or severity of the functional deficit.
		Controls*	(54–86)	Fellow eye-PED: 1 pt; CNV: 6 pts VA ≥6/12		

Owsley et al (2000)[237]	Case-control	Cases-80	74.5	Study eye-early ARM: 71 pts; CNV: 3 pts; GA: 6 pts. (Early ARM, atleast 5 large drusen >63μm and/or focal hyperpig; controls, normal fundus or <20 hard drusen of size <63 micron meters	HVF (modified for scotopic conditions) *(scotopic and photopic sensitivity)*	Mean retinal sensitivity was significantly lower in ARM pts when compared with controls. The deficit was maximum at 2 to 4 degrees of foveal ecentricity and decreased with increasing ecentricity. Greater degree of dysfuntion in DA sensitivity in fellow eyes of pts with unilateral AMD. No correlation was observed between DA retinal sensitivity and drusen extent.
		Controls-12	(59–91)	VA-Cases ≥20/60; Controls ≥ 20//30		
Owsley et al (2001)[238]	Case_control	Cases-20	75	Study eye-drusen (one or more >63μm) and/or focal hypering	HVF (modified for scotopic conditions) *(scotopic & photopic*	On average, patients with early ARM exhibited deficits in almost all rod-mediated parameters of DA when compared with controls.
		Controls-16		VA ≥20/25		
Haimovici et al (2002)[135]	Case-control	Cases-31	71	Study eye-macular drusen Fellow eye divided into 3 Groups Gr 1: RPE detachment/tear (11 eyes); Gr 2: CNV (10 eyes); Gr 3: Drusen (10eyes)	HVF (modified for scotopic conditions) *(scotopic sensitivity)*	Scotopic sensitivity was generally normal in pts with ARM. The time constant for DA was prolonged in pts with ARM and this dysfunction was maximum centrally and in pts with pts with RPE tear or detachment in the fellow eyes.
		Controls-11		VA≥6/9		
Scholl et al (2004)[273]	Cross sectional	17 pts	75	Study eye-drusen: 3 pts: extrafoveal CNV: 2pts; extrafoveal GA: 2. All study eyes have areas of increased fundus autofluorescence	HVF (modified for scotopic conditions) *(scotopic & photopic sensitivity)*	In areas of increased autofluroescence, the losses in scotopic sensitivity exceeded the photopic sensitivity losses. This suggests that areas of increased fundus autofluorescence in pts with pts with ARM correlate with functional losses.
			(68–80)	VA-20/20 to 20/40		
Jackson et al (2006)[152]	Case-control	Cases-19	74	Study eye-soft drusen and/or hyperpig or hypopig	Scotopic Sensitivity Tester-1 *(scotopic sensitivity)*	No significant difference was observed in the rate of DA between pts with ARM and elderly subjects with normal retina.
		Controls-29		VA-0.2		

*Not available. AMD: Age-related macular degeneration; ARM: Age-related maculopathy; CNV: Choroidal neovascularization; DA: Dark adaptation; GA: Geographic atrophy; HVF: Humphrey visual field analyser; Mo: Months; Pt(s): Patient(s); PED: Pigment epithelial detachment; RPE: Retinal pigment epithelium; UL: Unilateral eye; VA: Visual acuity.

detachment, and one eye developed GA. The findings of this small study suggested that loss of DA foveal sensitivity is an excellent predictor for the subsequent development of advanced ARM in eyes with drusen. Furthermore, a high incidence of RPE detachment may possibly be explained by the fact that there is a continuum between soft drusen and RPE detachment, and such RPE changes in early stages may be associated with a decrease in the absolute sensitivity at the fovea.

A decline in scotopic RS precedes loss of photopic RS in ARM patients, and this decrease in scotopic RS may or may not parallel associated loss of photopic RS. Furthermore, the loss in scotopic RS is greater in magnitude than photopic sensitivity loss in 87% of patients with early ARM,[153] and may exhibit significant regional variation. Of the two studies, which have investigated scotopic RS as a function of eccentricity, one has demonstrated a marked decrease close to the fovea,[49] whereas Owsley et al observed maximum deficit at the parafovea (2–4 degrees from the fovea).[237] Psychophysical studies have demonstrated that the adaptation mechanism in rod photoreceptors is compromised as far as 25 degrees eccentricity in the horizontal meridian.[49]

Two studies have investigated the relationship between the kinetic aspect of DA function and disease severity, in terms of drusen number and extent, and findings from both of these studies failed to demonstrate a meaningful relationship between these two variables.[237,297] DA function has also been evaluated in an attempt to identify eyes, which are at higher risk for developing subsequent neovascularization. Owsley et al demonstrated a greater degree of loss in scotopic RS in fellow eyes of patients with unilateral advanced ARM compared with control subjects, suggesting that scotopic RS may be used for prognostic purposes.[237] Similarly, Eisner and co investigators observed a significant delay in the time course for foveal photopic DA in the fellow eyes of 41 patients with unilateral CNV, with high-risk features, such as large drusen size, more than minimal drusen confluence, and focal hyperpigmentation.[106] In addition, the same investigators reported that the prolonged time course for DA, in combination with abnormalities in color-matching, is the most effective combination for identifying those eyes found to subsequently develop CNV; however, neither time course for DA alone nor color-matching alone appeared to be of prognostic value for CNV development.[105]

It is hypothesized that structural changes in Bruch's membrane, which are exaggerated in patients with ARM, where thickening of Bruch's membrane is seen, accompanied by reduced collagen solubility and deposition of neutral lipids, lead to retinoid deficiency with consequential impairment of rhodopsin regeneration and slowing of the kinetic aspect of DA function.[87] Indeed, Owsley et al, in a randomized double-masked and placebo-controlled study, demonstrated an increased rate of rod-mediated DA in 104 participants (41: normal retina; 45: early ARM; 18: intermediate ARM) following a 30-day course of 50,000 IU oral retinol.[239]

Alternatively, an abnormality of the ABCR gene product, which is a photoreceptor-based retinoid transporter, may limit the availability of 11-*cis*-retinal to the rod outer segment, thus resulting in prolongation of pigment regeneration.[301,340] However, it should be emphasized that mutation of the ABCR gene is not a major risk factor for ARM.[89] Lastly, progressive impairment of RPE metabolism may result from gradual accumulation of intracellular lipofuscin with senescence,[231,291] with a consequential impairment of the kinetic aspect of DA function.

Furthermore, a relative deficiency of retinoid may potentially explain the earlier involvement of rods relative to cones in ARM, because vitamin A deprivation leads to outer segment degeneration and photoreceptor death in vivo,[98,162,163] and accelerated degeneration of photoreceptors with mutant rhodopsin in vitro.[199] Such a lack of vitamin A primarily affects rods initially, although it does ultimately have an impact on cones.[61,165,166]

In conclusion, it is evident that patients with ARM exhibit a delay in the kinetic aspect of DA function that may or may not be associated with a parallel decrease in scotopic RS. This psychophysical observation is consistent with the findings from histopathological studies, which demonstrate a preferential vulnerability of parafoveal rod photoreceptors in early ARM. Furthermore, prolonged time course for foveal photopic DA, in combination with abnormalities of colour matching, may identify eyes at high risk for developing neovascular AMD. Lastly, absolute DA foveal sensitivity may detect RPE detachment at an early stage, with good degree of sensitivity and specificity.

B. THE PHOTOSTRESS TEST

1. Definition and Basic Principle

The photostress test (PST), also known as the *glare recovery* or *dazzling* test, refers to a technique of assessing the dynamic response of the retina following exposure to a controlled glare source, and measuring the time course for return of retinal sensitivity in terms of predefined visual tasks, the two common being VA and CS.[70] The test, first proposed by Bailliart in 1954 (*Ophthalmic Bulletin*, France 1954), provides an alternative and quantitative

means of evaluating physiological function at the macula.

Following photostress to the macula, there is a subjective appearance of a scotomatous afterimage, and a transient state of increase in the retinal threshold. It is hypothesized that the persistent afterimage may reflect either a relative deficiency of photopigment from its customary receptive site, or the presence of primary or secondary products of photolysis that have not been reconverted to receptive pigment.[48] Furthermore, the increase in retinal threshold is related to the density of photopigment within the cone photoreceptors, and increases by about 3 log units following total bleach.[264]

The recovery of visual function is believed to be largely due to regeneration of cone pigment,[123,280,360] and is presumably dependent on the anatomic and biochemical events that occur in the RPE-photoreceptor complex following the photopic process of vision.[6] It is believed that a higher degree of functional recovery is required for restoration of baseline VA than for CS. According to Severin et al, 95% of the normal subjects require less than 0.871 and 1.175 minutes to recover a defined function of contrast discrimination and VA, respectively.[279]

The PST is quantitative, involves precise delivery of the photic stress, and can be performed easily in an outpatient setting. However, it is seldom used as a clinical tool to diagnose or monitor macular diseases due to a lack of standardized techniques for performing the test and because of the wide variation in the observed recovery time.[70] Recently, the Eger Macular Stressometer (EMS; Gulden Ophthalmics, USA) is designed in an attempt to provide a standardized method for measuring photostress recovery time (PSRT). It is important to note that any macular disease is capable of altering the PST response, whether the primary pathology resides in the photoreceptors, the RPE, Bruch's membrane, or the choriocapillaris.

Several studies have investigated the age effect on PSRT in normal subjects; however, the results have been inconsistent. Some investigators have demonstrated a delay in PSRT with increasing age, approximately 0.19 log unit per decade of life;[267] however, many have failed to observe any such age effect on PSRT.[272,287,360] The reason for such inconsistency may be, at least in part, due to the lack of a standardized technique for carrying out the PST. Additionally, an increased variability in the responses from elderly subjects due to a decline in visual function, beginning at the age of 50 years, may compromise the comparability of PSRT results between subjects.

2. The Photostress Test and Age-related Maculopathy

Fourteen studies that have investigated PSRT in patients with ARM are summarized in Table 3.[23,64,66,70,117,123,221,267,268,272,279,287,357,360] All studies, except two,[272,357] have demonstrated a prolonged PSRT in patients with ARM, and, therefore, it is unsurprising that patients with ARM may become acutely symptomatic while going indoors on a bright day, driving through a tunnel in the daytime, or viewing oncoming headlights at night due to slow recovery of vision after exposure to glare.[267]

Schmitt et al examined PSRT in patients with ARM (30 eyes) and compared it with those having normal fundus or mild cataract (30 eyes), diabetic retinopathy (16 eyes), and glaucoma (16 eyes).[272] Although the authors concluded that PSRT distribution did not differ significantly among the subgroups, it was observed that the mean PSRT was greater in eyes with ARM (11.8 sec) when compared with other pathologies (normal or cataract: 10.0 sec; diabetic retinopathy: 8.4 sec; glaucoma: 8.6 sec). Furthermore, Wolffsohn et al, in a recent longitudinal study, failed to observe prolonged PSRT in 156 patients with advanced ARM. Of note, PSRT in both these studies was examined using EMS, and this may suggest that EMS in the current form is not a sensitive tool for measuring PSRT in patients with ARM.

Three studies have investigated the relationship between PSRT and ARM severity, in terms of drusen, pigmentary changes, and RPE atrophy; however, the results are inconsistent. Midena et al demonstrated a significant increase in PSRT with increasing drusen (number and confluence), pigmentary changes, and RPE atrophic changes in patients with ARM.[221] Furthermore, although Cheng et al did demonstrate a prolonged PSRT with pigmentary changes involving the macula, the authors failed to find a positive association between PSRT and drusen confluence.[64] Smiddy et al, in a group of 71 patients with bilateral drusen, failed to observe an association between PSRT and ARM severity.[287]

Sandberg et al have investigated the value of PSRT as a prognostic indicator of severe ARM by evaluating the PSRT for the fellow eyes of 133 patients with unilateral neovascular AMD and for five normal subjects.[267] The study eyes had a best-corrected VA of 20/60 or better, clear media, macular drusen, central fixation, and no other associated retinal disease. A delay in the PSRT was observed in 62% of patients, and was increased up to six times the upper limit of normal, suggesting that this test may be of prognostic value for CNV development. Furthermore, the same investigators, in a subsequent longitudinal study, demonstrated that a slow PSRT is an independent

TABLE 3

Studies Which Have Investigated Photostress Recovery Time in Patients with Age-related Mculopathy

Principal Investigator/Year of Publication	Type of Study	Sample Size	Age in Yrs Mean/range	ARM Status and Visual Acuity	Instrument/ Details of Light Source	Outcome Measure	Conclusion
Chilaris et al (1962)[66]	Case report	1 pt	62	Study eye-early ARM (pig changes) Fellow eye-normal fundus VA-RE: 6/10; LE: 10/10	Direct ophthalmoscope 30 sec	VA	PSRT was prolonged in the ARM eye when compared with normal fellow eye.
Severin el al (1963)[279]	Case-control	Case-1 Controls-57	57 32 (23–41)	Study eye -ARM status*, fellow eye normal VA-RE: 20/70; LE: 20/20	Zeiss light coagulator 242,600 lux	VA and contrast threshold	A prolonged PSRT was observed in both eyes of ARM pts (study eye > fellow eye) when compared with controls.
Forsius et al (1963)[117]	Case-control	Cases -* Controls-402	*	Study eye -CNV: 3 pts; GA:*	Keeler ophthalmoscope 2145 lux, 15 sec, 30 cms	VA	GA, irrespective of VA, was associated with normal PSRT. Of the 3 pts with CNV, one had prolonged PSRT.
Glaser et al (1977)[123]	Case-control	Cases-29 Controls-179	* (16–78)	Study eye-drusen, 11 pts; AMD, 18 pts VA-6/6 to 6/12	Penlight 20 sec, 2–3 cms	VA	A prolonged PSRT was observed in all pts with AMD and 7 pts with drusen (63.63%).
Smiddy et al (1984)[287]	Prospective (51.6 mo)	71 pts	57.7	Study eye-drusen and/or pig changes BE tested independently VA-20/15 to 20/100	Penlight 20 sec, 2 inches	VA	PSRT did not correlate with severity of drusen, decreasing visual acuity or increasing age
Collins et al (1989)[70]	Case-control	Cases-21 Controls-11	66.6 65.8	Study eye-hard drusen and/or pig changes. VA-controls: ≥6/6; case: ≥6/6 (pre ARM, 11 pts) and 67.5 or worse (ARM, 10 pts)	Floodlight 500 W, 10 sec	Contrast threshold	PSRT was significantly prolonged in cases, both pre ARM and ARM, when compared with controls. However, pts with ARM demonstrated a significant delay in the recovery times than pre ARM during the middle and late phases of recovery.
Wu et al (1990)[360]	Case-control	Cases-17 Controls-18	72 (59–79) 47.1 (18–77)	Study eye-soft or hard drusen VA-controls: 20/15 to 20/40; cases: 20/25 to 20/70	Indirect ophthalmoscope 6 volts, 10 sec, 10 cms	VA	PSRT was significantly greater in pts with ARM than controls. The recovery time did not increase with age or worsening of VA
Cheng et al (1993)[64]	Case-control	Cases-22 Controls-8	60-85	Study eye-hard drusen and/or pig changes (pre ARM, 11 pts) and/or confluent drusen (ARM, 11 pts). VA-controls: ≥ 6/6; pre ARM: ≥ 6/7.5; ARM: 6/7.5 to 6/15	QI light 24 volts, 20 sec, 40cms	VA (near)	Pts with ARM have prolonged PSRT when compared with pre ARM and controls. Also, there was a significant positive relationship between pig change at the macula and prolonged PRST.

Sandberg et al (1995)[267]	Cross sectional	133 pts	74	Study eye-fellow eyes of pts with UL CNV consisting of drusen VA ≥ 20/60	Welch Allyn Finnoff ocular transilluminator in trial frame 6 log troland, 10 sec	VA	Prolonged PRST in the fellow eyes of patients with UL CNV. PSRT increases with decreasing VA and in presence of foveal RPE atrophy.
Midena et al (1997)[221]	Case-control	Cases-47	65.30 (51–74.5)	Study eye-BE ARM: 34 pts; fellow eye of pts with UL AMD: 13pts. Early ARM was defined by the presence of soft drusen ≥ 63 μm and/or pig changes and/or RPE atrophy.	Nictometery (Registriert)	VA	Pts with ARM have prolonged PSRT when compared with controls. Drusen number & confluence, focal hyperpig and RPE atrophy were related to a significant increase in PSRT; however, there was no difference in PSRT between eyes with bilateral ARM and fellow eyes of pts with UL AMD.
		Controls-36	64.33 (51–75)	VA ≥ 20/25			
Sandberg et al (1998)[268]	Prospective (4.5 years)	127 pts	58–89	Study eye-fellow eyes of patients with UL CNV consisting of drusen (hand/soft), pig changnes and RPE atrophy VA 20/20 to 20/60	Welch Allyn transilluminator 10 sec	VA using computer	A slow PSRT appears to be an independent risk factor for development of CNV in the fellow eyes of pts with UL CNV. The relative risk increased by a factor of 30% for each minute of glare recovery time.
Schmitt et al (2003)[272]	Cross sectional	30 pts	73.3	Study eye-ARM severity was graded using AREDS categories (Gr 1:1 pt: Gr 2: 6 pts; Gr 3: 11 pts; Gr 4: 12 pts) VA = 20/80	Eger macular stressometter	VA	PSRT was normal in pts with ARM probably due to lack of sufficient photostress to the retina by the EMS suggesting that EMS in current form is not a sensitive tool for ARM. PSRT was not related to age, sex, and visual acuity.
Bartlett et al (2004)[23]	Case-control	Cases-29	70.2 (57.5–80)	Study eye-ARM, soft drusen and pig changes: 17 pts: AMD, GA or CNV: 12 pts.	Eger macular stressometer	VA	A statistically significant delay in PSRT was observed in pts with ARM when compared with controls suggesting that EMS may be a useful screening test for ARM; however, illumination with greater intensity and longer duration may yield less variable results.
		Controls - 49	44.6 (18.76)	Va-Controls: = 0.1; ARM: -0.1–0.2; AMD: 0.2–0.7.			

(*Continued*)

Table 3 (*Continued*)

Principal Investigator/Year of Publication	Type of Study	Sample Size	Age in Yrs Mean/range	ARM Status and Visual Acuity	Instrument/ Details of Light Source	Outcome Measure	Conclusion
Wolfisohn et al (2006)[357]	Prospective (1 year)	156 pts	78.9	Study eye-CNV: 90 pts; GA: 19 pts; CNV plus GA: 47 pts VA-CNV: 0.6: GA: 0.0: CNV plus GA: 0.0	Eger macular stressometter	VA	PSRT was normal in pts with ARM and did not correlate with visual function measures (contrast sensitivity and VF defect) and subjective difficulities in vision with changing levels of light. Also, no significant difference was observed in PSRT in ARM eyes with decreased VA over 1 year period compared to those where VA remained unchanged.

* Not available. AMD: Age-related macular degeneration; ARM: Age-related maculopathy; BE: Both eyes; CNV: Choroidal neovascularization; GA: Geographic atrophy; LE: Left eye; Mo: Months; Pt(s): Patient(s); PSRT: Photostress recovery time; RPE: Retinal pigment epithelium; RE: Right eye; UL: Unilateral eye; VA: Visual acuity.

risk factor for developing CNV in the fellow eyes of patients with unilateral CNV, and the risk increases by a factor of 30% for each minute of delay in the PSRT.[268]

Interestingly, Collin et al have observed a relatively greater degree of PSRT prolongation in ARM patients with reduced VA when compared with ARM patients with normal VA (the authors described these patients as pre ARM patients).[70] Enoch et al hypothesized that ARM progresses towards the inner layers of the retina, first affecting the sustained-response mechanism of the outer retina and later involving the transient-response mechanism of the inner retina.[111] The authors hypothesize, therefore, that because glare recovery involves a transient stimulus, ARM patients will have a greater impairment of this transient response mechanism than pre-ARM patients due to inward spread of the disease.

It is evident that there is a prolonged PSRT in patients with ARM, and Collin et al have proposed two mechanisms to explain this.[70] Age-related maculopathy, in particular GA, is believed to be associated with attenuation of the choriocapillaris, with an associated reduction in the choroidal blood flow, and diminished metabolic activity of the RPE cell layer. As this cell layer is essential for regeneration of photopigment,[5] the impairment of PSRT in patients with ARM is unsurprising. Alternatively, dysfunction of photoreceptor membranes may play a role in prolonged PSRT in ARM patients. The reason being that, following exposure to a glare source, there is temporary destabilization of the free-radical auto regulatory mechanisms that maintain optimum functioning of the photoreceptor membranes by preventing free radical induced oxidative stress.[181]

In conclusion, patients with ARM have significant delay in the PSRT when compared with normal subjects. Furthermore, the measured recovery time appears to parallel disease progression, and may have the potential to identify eyes at particularly high risk for developing neovascular AMD.

IX. Perimetry

A. DEFINITION AND BASIC PRINCIPLE

The term *perimetry* is used almost interchangeably with visual field testing, and dates back to fifth century B.C.E. when Hippocrates first described a hemianopic defect.[46] This psychophysical test measures the visual function of the eye at topographically defined loci in the visual field. Perimetry is based on the concept of visual threshold testing, and constitutes an integral component for the diagnosis and management of various eye diseases.

The visual field (VF) is that portion of the external environment of an observer wherein the steadily fixating eye(s) can detect visual stimuli, and in normal subject extends 110 degrees temporally, 60 degrees superiorly (limited by the supraorbital margins), 65 degrees nasally (limited by the nasal bridge), and 75 degrees inferiorly.[204] In three-dimensional view, the VF is represented as a "hill of vision" (also known as *Traquair's island*), with peak sensitivity at fixation and a gradual decline towards the periphery. The regional/zonal variation in the sensitivity within the VF depends on the heterogeneous distribution of the specialized sensory cells in the retina, and their neural connections, along with a gradation in the ratios of the photoreceptors to ganglion cells.

Furthermore, when VF is mapped topographically on the surface of the striate cortex, the projection is larger for the central VF, and decreases progressively towards the peripheral VF.[226,278] In other words, there is a decreasing amount of visual cortex devoted to each degree of the VF as one proceeds from the fixation into the periphery. According to De Valois et al, the eventual cortical magnification of the central retina is such that approximately 25% of the striate cortex is devoted to the processing of the central 2.5 degrees of the VF.[91]

Conventional perimetry, also known as white-on-white perimetry, is the most common form of static perimetry used in the clinical setting, and involves presentation of white spots of light on a white background. The two main limitations of conventional perimetry include poor test–retest variability, particularly in areas of VF loss,[19,350,351] and the inability to represent adequately the extent of neural damage.[140,141,167,248] In recent years, conventional perimetry has evolved substantially, in part due to advances in computer technology that enables more complex visual stimuli and test algorithms. Flicker perimetry, fundus perimetry, SW automated perimetry (SWAP), and frequency-doubling technology (FDT) perimetry are the four recently developed techniques that may prove invaluable in the evaluation of patients with ARM.

Flicker perimetry, which utilizes the luminance pedestal flicker stimulus, measures the contrast threshold for a fixed temporal frequency, and is also known as temporal modulation perimetry.[9] It is believed that the low-frequency luminous pedestal, created for the stimulus duration, affects detection threshold[8] either by invoking local adaptation and contrast dependent masking effects[9,10] or by rod–cone and cone–cone interactions from the surrounding retina.[10,68,69,102,124] Flicker perimetry is relatively robust to the effects of blur and pre-retinal absorption when compared with conventional perimetry.[176] Therefore, it is reasonable to suggest that this form of perimetry would be more useful for VF assessment in elderly patients with ARM. However, it is essential to give clear instructions and a practice trial before actual readings are measured in order to avoid a high number of false positive responses with flicker perimetry.

Fundus perimetry, also known as microperimetry, allows exact correlation between individual fundus lesions and corresponding functional defects via integrating fundus imaging and computerized threshold perimetry. Fundus perimetry can be performed using SLO, but this technique lacks important software features (such as real-time fundus tracking), covers limited field of view, and is no longer available commercially. Recently, the Microperimeter 1 (MP 1, Nidek Technologies, Padova, Italy) has been introduced that allows fundus perimetry in a larger field, using automated full threshold perimetry, with simultaneous acquisition of a real colour fundus image. Similar to the SLO, MP 1 can correct for eye movements but unlike the SLO it uses an automated tracking system. Furthermore, fundus perimetry using the MP 1 automatically and accurately maps the location and quality of fixation in patients with ARM.

SWAP measures the sensitivity of the SW sensitive visual pathways by using the Stiles two-color threshold method. SWAP utilizes a blue stimulus (Goldmann size V, peak transmission at 440 nm) to preferentially stimulate the blue S-cones system, and a high luminance yellow background to adapt the green M- and red L-cones system and decrease their sensitivity.[216] SWAP has the advantage of indicating early damage in patients with ocular hypertension and glaucoma;[156–158] however, a recent study demonstrated that SWAP in its existing form is markedly less efficient than conventional perimetry in detecting glaucomatous VF defects.[290] Furthermore, SWAP is limited clinically by greater inter-individual variability of threshold,[33] increased test duration, and an additional learning curve. Lastly, SWAP exhibits significant absorption by ocular media,[349] thus rendering it unsuitable for many elderly patients with ARM because of co-existing lens opacity.

Frequency-doubling technology perimetery is based on the frequency-doubling effect, where the SF of a coarse grating stimulus appears to double when the gratings are flickered counter phase at a rapid rate (25 Hz).[164] This perimeter uses 10° square grating as stimuli (in contrast to the small size stimuli used in conventional perimetry) that restrict the spatial ability to localize VF defects. FDT may be an invaluable tool for detecting VF defects in elderly patients because this technique has a very

TABLE 4

Studies Which Have Investigated Visual Fields in Patients with Age-related Maculopathy

Principal Investigator/Year of Publication	Types of Study	Sample Size	Age in Yrs Mean/range	ARM Status and Visual Acuity	Instrument/Name of the Test	Conclusion
Cambell et al (1959)[58]	Cross-sectional	63 pts	*	ARM status* VA ≥ 20/25, 23 pts; 20/25, 21 pts; 20/50 to 20/200, 19 pts	Tangent screen (at 6 mts)	There was a predominance of a paracentral defect in ARM pts with VA ranging from 6/7 to 6/15. However, central and paracentral defects were observed with equal frequency when ARM pts have VA < 6/15.
Greve et al (1976)[130]	Cross-sectional	20 pts	60–68 approx	Study eye-ARM was graded from 1 to 4 Gr 1:drusen Gr 2a confluent drusen; Gr 2b:?PED + subfoveal fluid; Gp 3:PED with subfoveal fluid; Gp 4:CNV VA-1.0 to <0.5	Tubinger perimeter photopic (3.12 cd . m^{-2}) & mesopic (0.00312 $cd.^{m-2}$) perimetry	An increase in mesopic/photopic ratio indicates intensification of defects at mesopic levels, and suggests the presence of sub RPF or sub retinal fluid.
Greve et al (1979)[129]	Prospective (3-30mo)	68 pts	53–80 approx.	Study eye-ARM was graded from 1 to 4 Gr 1:drusen Gr 2a confluent drusen; Gr 2b:?PED + subfoveal fluid; Gp 3:PED with subfoveal fluid; Gp 4:CNV VA*	Tubinger perimeter photopic (3.12 cd . m^{-2}) & mesopic (0.00312 $cd.^{m-2}$) perimetry	Isolated drusen do not cause VF defects. Confluent drusen may show VF defects with mesopic intensities greater than photopic due to early involvement of rod system. During follow up mesopic defects almost always deteriorate before photopic defects
Hart et al (1983)[139]	Case report	2 pts	64 and 69	Study eye-CNV:1pt; GA:1pt VA-CNV:20/50; GA: 20/25	Goldmann perimeter with static mode central 10 degrees	Perifoveal depression of VF with a distinct preservation of sensitivity at the point of fixation
Atchison et al (1990)[20]	Case control	Cases-15	63.5 (58–68)	Study eye-hard drusen and/or fine pig stippling and/or hypo pig at the macula	HVF 24-2 and central 10-2	No significant difference in MS between pts with ARM and controls, suggesting that hard drusen and fine pig changes may be regarded as normal ageeing changes.
		Controls-15	63.3 (59–67)	VA-6/6		
Swann et al (1991)[309]	Case control	Cases-20	66.5	Study eye-drusen and/or pig changes (pre ARM, 10 pts) and/or serous PED (ARM, 10 pts)	Friedmann VF analyser and autoplot tangent screen	Pts with ARM exhibit paracentral scotomata, with preservation of foveal sensitivity; however, no VF defect was seen in pts with pre ARM. Pig changes may lead to VF defects (40%) but areas of soft and/or hard drusen failed to exhibit such defect.
		Controls-10	64.8	VA-pre ARM ≥ 6/6; ARM <6/6		

Cheng et al (1993)[64]	Case-control	Cases-22	60–85	Study eye-hard drusen and/or pig changes (pre ARM, 11 pts) and/or confluent drusen (ARM, 11 pts)	HVF Central 10-2	Although ARM pts had reduced sensitivities, the differences in the MS of ARM, pre ARM, and controls failed to reach statistical significance. Also, 4 ARM and 4 pre ARM pts exhibited a central VF defect, whereas no such defect was observed in controls.
		Controls-8		VA-controls: ≥ 6/6; pre ARM: ≥ 6/7.5; ARM:6/7.5 to 6/15		
Tolentino et al (1994)[319]	Cross-sectional	59 pts	72.3	Study eye-dry AMD consisting of RPE atrophy (ranging from patchy hypopig to demarcated GA of RPE) and/or drusen with intact central fixation. Fellow eye-CNV:43 patients VA ≥ 20/40	HVF Macular threshold test	Visual field defects correlate significantly with areas of RPE atrophy but not with areas of drusen.
Midena et al (1994)[222]	Case-control	Cases-35	64.9	Study eye: ARM consisting of ≥ 10 drusen within 1500 μm of foveal centre in both eyes.	HVF Central 10-2	Statistically significant difference in MS between pts with ARM and controls. Also, MS was significantly worse in association with large and soft drusen, but not with drusen number.
		Controls-16	65.8	VA -20/20		
Midena et al (1997)[221]	Case-control	Cases-47	65.30 (51–74.5)	Study eye-BE ARM:34 pts fellow eye of pts with UL AMD: 13pts. Early ARM was defined by the presence of soft drusen 63 μm and/or pig changes and/or RPE atrophy.	HVF Central 10-2.	MS of central VF was significantly lower in ARM pts when compared with controls, and was significantly influenced by number of drusen, focal hyperpig, and RPE atrophy. There was no significant difference in MS between eyes with bilateral ARM and the fellow eyes of pts with UL AMD.
		Controls-36	64.33 (51–75)	VA ≥ 20/25		
Takamine et al (1998)[312]	Cross-sectional	19pts	68.5 (42–86)	Study eye-drusen: 15pts; drsuen with CNV: 3 pts; drsuen with PED: 1 Fellow eye-CNV: 7 pts VA*	Fundus primetry (SLO) retinal sensitivity over drusen	Large drusen, defined as drusen with clear borders, were associated with a statistically significant decrease in retinal sensitivity. Also, no relationship between drusen size and the amount of loss of retinal sensitivity was observed.
Remky et al (2001)[255]	Cross-sectional	126 pts	71 (55–87)	Study eye-drusen and/or hyperpig and/or atrophic area <200 μm VA>20/50	SWAP central 10 degrees	There was a significant decrease of SWS sensitivity in eyes with risk factors for ARM such as presence of soft drusen and fellow eyes with AMD. Focal hyperpig was associated with a significant loss in sensitivity for the central 5 degree.

(*Continued*)

Table 4 (*Continued*)

Principal Investigator/Year of Publication	Types of Study	Sample Size	Age in Yrs Mean/range	ARM Status and Visual Acuity	Instrument/Name of the Test	Conclusion
Phipps et al (2004)[245]	Case-control	Cases-25	69.4	Study eye-soft drusen (>5)with/with out pig changes. Fellow eye-CNV, 7pts Controls-subjects with < 5 hard drusen and no focal hyperpig	Automated perimeter with flickering stimulus	Pts with early ARM have larger and deeper defects for flickering than static targets suggesting that flickering targets may detect VF deficts in early ARM better than do static targets.
		Controls-34		VA > 6/12		
Remky et al (2005)[254]	Case-control	Cases-24	70 (62–78)	Study eye-drusen (hard: 13 eyes soft 10 eyes) and/or pig changes and/or atrophic area <200 μm	SWAP (SLO) central 10 degrees	SWS cone sensitivity was significantly reduced in pts with ARM than controls, and this loss in sensitivity was diffuse as well as localized to the areas of drusen. Also, pts with soft drusen had lower sensitivity than those with hard drusen
		Controls-24	68 (60–76)	VA ≤ 20/40		
Feigl et al (2005)[114]	Case-control	Cases-13	63–77	Study eye-early ARM, defined as small hard or soft distinct and indistinct drusen ≥ 63 μm with or without RPE changes	HVF central 10-2	Mean sensitivity of the central VF was within normal range in pts with ARM
		Controls-13		VA-6/6 to 6/12		
Midena et al (2007)[223]	Cross-sectional	13 pts	76.2	Study eye-early ARM, defined as small drusen (≤ 63 μm) and at least 5 or more intermediate soft drusen > 63 μm and/or large (either confluent) soft drusen (> 125 μm) localized within 3000 μm from fovea and/or pigment abnormalities	Fundus perimetry (Micro perimeter 1)	Retinal sensitivity was significantly decreased over large drusen when compared to retinal areas where drusen were absent. Similarly, retinal sensitivity was significantly decreased over pigment abnormalities when compared to retinal areas where such changes were absent. Furthermore, the reduction in retinal sensitivity was higher over areas where large drusen were associated with pigment abnormalities.

*Not available. AMD: Age-related macular degeneration; ARM: Age-related maculopathy; CNV: Choroidal neovascularization; GA: Geographic atrophy; Gr: Grade; HVF: Humphrey visual field analyser; MS: Mean sensitivity; Mo: Months; Pt(s): Patient(s); PED: Pigment epithelial detachment; RPE: Retinal pigment epithelium; VF: Visual field; VA: Visual acuity; Yrs: Years.

short testing time, and is resistant to optical blur and pupil size.[234] Furthermore, several studies have demonstrated that the FDT perimeter has good sensitivity and specificity for detecting glaucomatous field defects,[62,241,314,323,361] but few investigators have evaluated its role in ARM patients.[282]

Recently, a second-generation FDT instrument (FDT 2; Humphrey Matrix, Carl-Zeiss Meditec Dublin, CA, USA) has become available. The small size of its stimuli (5° square grating) permits a larger number of VF locations to be examined, thus providing greater detail of the spatial distribution of VF loss. In addition, thresholds are estimated by a maximum-likelihood strategy,[325] which by presenting a constant number of four stimuli at each location ensures uniform test duration independent of the level of field loss.

B. VISUAL FIELDS AND AGE-RELATED MACULOPATHY

The details of 16 studies that have investigated VF in patients with ARM are summarized in Table 4.[20,58,64,114,129,130,139,221–223,245,254,255,309,312,319] The data from all these studies, except two,[20,114] have demonstrated that early ARM is associated with a decrease in the mean retinal sensitivity in the central VF. Furthermore, the VF defect appears to be most prominent in the parafoveal region, and spares fixation until end-stage disease.

Five studies have correlated retinal sensitivity with ARM disease severity, measured in terms of drusen (type, number, confluence), pigment alteration, and atrophic changes in the RPE. Greve et al, using differential perimetry, have demonstrated that confluent drusen may be associated with VF defects, and that such defects are relatively more intense at mesopic than photopic levels, perhaps due to early involvement of rod photoreceptors.[129] Similarly, Midena et al have observed a worsening of mean retinal sensitivity in the central 10 degrees of VF in eyes with large soft drusen, but the observed defect was not related to drusen number.[222] Furthermore, the same investigators, in a subsequent study, demonstrated that mean sensitivity (MS) of the central VF was significantly and adversely influenced by drusen number, focal hyper pigmentation, and RPE atrophy.[221] The two other studies, which have investigated retinal sensitivity with respect to disease severity, failed to demonstrate a meaningful relationship between sensitivity of the central VF with drusen, but did observe an association with pigmentary and/or atrophic changes.[309,319]

Conventional perimetry is not suited to measure retinal sensitivity over individual retinal lesions, in particular drusen, because of the small size of such lesions. Takamine et al assessed retinal sensitivity over individual drusen in 23 eyes of 19 patients with microperimetry using a scanning laser ophthalmoscope.[312] The investigators demonstrated a statistically significant decrease in retinal sensitivity of more than 5 decibels (dB) over large drusen (amorphous substance with a clear border) as opposed to soft drusen (amorphous substance with indistinct border). However, no relationship was observed between the size of the drusen and the amount by which the sensitivity was depressed. This suggests that photoreceptor dysfunction may be due to the result of an unknown biochemical effect associated with large drusen rather than the extent of separation of the RPE from the choriocapillaris.

Also, Midena et al, in a recent study, examined retinal sensitivity over areas of drusen and pigment abnormalities, using the Microperimeter 1, in 13 patients with early ARM.[223] The data demonstrated a statistically significant decrease in retinal sensitivity over large drusen and pigment abnormalities, and this reduction in retinal sensitivity was higher in patients where a combination of large drusen and pigment abnormalities were present. Additionally, retinal sensitivity was significantly decreased in retinal areas with altered fundus autofluorescence (recorded using SLO), when compared to retinal areas with normal autofluorescence in the same patients. These findings suggest that retinal sensitivity diminishes in areas underlying drusen and pigment abnormalities, in spite of good VA, in early ARM.

Furthermore, in patients with early ARM, a flickering stimulus may detect VF deficits better than static stimulus (e.g., more sustained targets) used in conventional perimetry because a flickering stimulus may stress retinal capacity to a greater degree than does a more sustained stimulus.[245] An alternative explanation for early VF loss detected by flicker perimetry may be a selective predilection for involvement of magnocellular/spatiotemporal pathways. This premise is further supported by mid-temporal frequency losses observed in patients with early ARM.[214,215]

Phipps et al compared static and flicker perimetry outcomes in 25 patients with early ARM and age matched control subjects.[245] They observed that flickering perimetry produces larger and deeper defects than static perimetry, with 52% of ARM patients having large VF defects and 84% of ARM patients having localized depression of greater than 10 dB in the foveal region. This suggests that a selective sensitivity loss to a flickering target may be present in the early stages of the ARM disease

process and may serve as an indicator of risk for progression to advanced disease.

The changes in the SW cone sensitivity can be used for early detection of glaucoma and damage by a variety of retinal diseases, such as retinitis pigmentosa and diabetic macular edema. Remky et al examined SW cone sensitivity in 126 patients with ARM using a conventional perimeter modified for SWAP, and demonstrated a significant decrease in mean SW cone sensitivity in the presence of three important risk factors and/or features of this condition: age, soft drusen, and advanced ARM in the fellow eye.[255] In contrast, focal hyperpigmentation resulted in loss of sensitivity in the central five degrees without a significant reduction in MS of the entire central field. Furthermore, the same authors investigated SW cone sensitivity in 24 ARM patients in a case-controlled fashion with SWAP, using a SLO on this occasion.[254] SW cone sensitivity was significantly reduced in patients with ARM when compared with controls, and this loss in sensitivity was both diffuse, and localized to areas of drusen.

In patients with ARM, loss of SW cone sensitivity may reflect early pathological changes to the photoreceptors, when these metabolically active cells receive reduced levels of oxygen and other metabolites, or accumulate waste products locally. Furthermore, evidence of drusen, in particular confluent drusen, may indicate local or diffuse dysfunction of the RPE, and pronounced loss of SW cone sensitivity with soft drusen is therefore consistent with the associated loss of metabolic and/or hydrophilic barrier function.

A study by Sheu et al investigated the role of FDT, using full-threshold C-20 mode, in 30 patients with the neovascular form of AMD,[282]and demonstrated that FDT is not sensitive enough for the detection of small neovascular lesions within the central 3 degrees in AMD patients. These investigators suggested a further modification of the existing FDT central target in order to detect small neovascular lesions. Furthermore, a recent study demonstrated that VF defects with FDT were very similar to those obtained with conventional perimetry; however, this observation was based on a single eye of an ARM patient.[7]

In conclusion, early ARM is associated with a central VF defect, which begins in the parafoveal zone and spares fixation until the late stages of disease. Furthermore, recently developed new techniques of perimetry, such as flicker perimetry, may identify eyes that are at increased risk for progression to neovascular AMD. Lastly, this psychophysical measure may be of value for the purpose of visual rehabilitation, by determining the size and position of the VF defect, thus guiding tasks such as reading and mobility.

X. Color Vision

A. DEFINITION AND BASIC PRINCIPLE

Color vision (CV) represents the ability to discriminate between stimuli, which differ in spectral composition, regardless of other dimensions such as intensity. External objects reflect a variety of wavelengths and the observer constructs a color percept based on the photoreceptor responses to the wavelength distribution and spatial variables.[310] Impairment of CV may be one of the earliest detectable changes in the visual process in the presence of retinal disease.

The three types of cone photopigment, each with different spectral sensitivity, are universally acknowledged to be the foundation of human trichromatic CV. The photopigments reside in the outer segments of cones, which are frequently referred as long-, medium-, and short- wavelength sensitive cones according to the relative spectral positions of their peak sensitivities (for retinal level [as opposed to corneal level]: long [L]: 558.9 nm; medium [M]: 530.3; short [S]: 420.7).[299] It is important to note that the peak density of L- and M-cones exist at the fovea, whereas the S-cones, which constitute 8–10% of the photoreceptor population,[171,209] are very sparse at the foveal center (so causing a S-cone blind spot) but peak in concentration at the foveal slope.[353] Various theories have been put forward for the processing of chromatic information at retinal and higher cortical levels, and a detailed description of these is beyond the scope of this discussion.

A CV test examines the ability of an observer to discriminate the distribution of different wavelengths, and describes a defect in terms of abnormalities in color matching, color discrimination, color arrangement, and spectral sensitivity. The color matching is frequently tested with an anomalscope, where a circular field is divided into two semicircles and the investigator makes adjustments in such a way that the colors match in the two semicircles for a given patient. Besides providing information about defects in CV, this technique may be used to reveal the spectral sensitivities of the cones, and for assessment of the integrity of cone outer segments.

Of the other commercially available CV tests, the Farnsworth-Munsell 100 hue test of color discrimination provides valid and quantitative information on color discrimination with a tendency to correlate well with other measures of CV performance. However, in clinical practice, the Farnsworth D-15 test is more commonly employed because it is easy and rapid to use. It is important to note that proper testing conditions are crucial for conducting all types of CV tests, such as standard illumination levels (referred to as Commission Internationale de 1'Eclairage Standard Illuminant C).

TABLE 5

Studies Which Have Investigated Chromatic Function in Patients with Age-related Maculopathy

Principal Investigator/Year of Publication	Type of Study	Sample Size	Age in Yrs Mean/range	ARM Status and Visual Acuity	Name of the Test/ Instrument	Conclusion
Bowman KJ (1978)[39]	Case-control	Cases-15 Controls-10	66.5 64	ARM* VA: 6/6 -6/12, 8 pts; <6/12 -6/30, 7 pts	FM 100	Pts with ARM have a blue-yellow defect, which decreases in severity with increasing illumination.
Bowman KJ (1980)[38]	Case-control	Cases-15 Controls-10	66.5 64	ARM* VA: 6/6 -6/12, 8 pts; <6/12 -6/30, 7 pts	FM 100 and Panel D-15	Deterioration of color discrimination with luminance is more marked in pts with ARM when compared with controls.
Bowman et al (1984)[40]	Case-control	Cases-10 Controls-10	74.3 73.2, 21.3	ARM* VA: 6/18 -6/60	Panel D-15, Desaturated D-15 and H-16	Color discrimination is adversly affected in pts with ARM compared with age matched controls and young controls.
Collins MJ (1986)[71]	Case-control	Cases-21 Controls-11	66.6 65.8	Study eye: drusen and/or pig changes VA ≥ 6/6, pre ARM (11 pts); <6/6, ARM (10 pts)	Desaturated D-15	Color discrimination is diminished in pts with pre ARM and ARM, with a tendency towards a tritan defect.
Applegate et al (1987)[12]	Prospective (*)	3 pts	64 (53–73)	Four study eye-drusen VA ≥ 20/25 2 patients have CNV in the fellow eyes	FM 100 and Panel D-15	A large reduction in blue chromatic processing are seen in early ARM. These losses increase over time and accelerate at or near the time of progression to advanced ARM.
Smith et al (1988)[288]	Cross-sectional	10 pts	61 (50–78)	Pts divided into Sarks grade II (3 pts); III (4 pts); IV (3 pts) VA ≥ 6/6 to 6/18	Moreland anomaloscope	Pts with ARM have abnormalities of color matching, and this may be attributed to abnormalities in the orientation of the photoreceptor layer.
Atchison et al (1990)[20]	Case-control	Cases-11 Controls-13	63.5 (58–68) 63.3 (59–67)	Study eye-ARM: hard drusen and/or pig changes (hypo or hyper pig) VA ≥0.0	Desaturated D-15	No significant difference in color discrimination between pts with ARM and controls.
Eisner et al (1991)[106]	Cross-sectional	41 pts	≥ 60	Fellow eyes of patients with UL CNV (Drusen and/or hyperpig and/or atrophy) VA ≥20/25	Farnsworth Panel D-15, color matching (Rayleigh color match)	High risk eyes (confluent large drusen with hyper pig) were associated with abnormal colour matching and failed D-15 testing.
Eisner et al (1992)[105]	Prospective (18 mo)	47 pts	55–86	Fellow eyes of patients with UL CNV (Drusen and/or heperpigmentation and/ or atrophic areas) VA ≥20/25	Farnsworth Panel D-15, color matching (Rayleigh color match)	Color matching in combination with dark adaptation was the most effective means for distinguishing those eyes found to subsequently develop CNV.

(*continued on next page*)

Table 5 (*continued*)

Principal Investigator/Year of Publication	Type of Study	Sample Size	Age in Yrs Mean/range	ARM Status and Visual Acuity	Name of the Test/ Instrument	Conclusion
Cheng et al (1993)[64]	Case-control	Cases-22 Controls-8	60–85	Study eye-hard drusen and/or pig changes (pre ARM,11 pts) and/or confluent drusen (ARM,11 pts). VA-controls:≥ 6/6 pre ARM:≥ 6/7.5; ARM: 6/7.5 to 6/15	Farnsworth Panel D-15 test, desaturated panel D-15 test and Iso-value color vision test	Eyes with ARM demonstrated a blue yellow defect along with a positive relationship between confluent drusen and losses in color saturation and hue discrimination. However, pre ARM pts failed to demonstrate a definitive color vision defect.
Frennesson et al (1995)[118]	Case-control	Cases-27 Controls-27	69.7 (57–80) 67.7 (51–79)	ARM-soft drusen (some confluent) and/or pig changes (no clumping) Fellow eye-CNV (8 patients) VA: 0.9 to 1.0	Color contrast sensitivity using computer graphics system	The color contrast sensitivity showed a deterioration in color discrimination for tritan axis, as well as for protan and deutan axes in ARM pts. Increased tritan threshold for high risk group, although statistically insignificant.
Holz et al (1995)[147]	Prospective (24 mo)	84 pts	68.89 (55-84)	ARM-unilateral or bilateral drusen VA = 6/9	Color contrast sensitivity using computer graphics system	The mean tritan threshold was markedly elevated at the fovea compared with parafovea. Pts who subsequently developed advanced ARM had higher tritan threshold at the fovea than pts who did not develop such lesions.
Midena et al (1997)[221]	Case-control	Case-47 Controls-36	65.30 (51-74.5) 64.33 (51-75)	Study eye-BE ARM: 34 pts fellow eye of pts with UL AMD: 13 pts. Early ARM was defined by the presence of soft drusen = 63 μm and/or pig changes and/or RPE atrophy. VA = 20/25	FM 100	No detectable deficit in CV was observed in pts with ARM.
Arden et al (2004)[17]	Case-control	Case-24 Controls-109	76 71.5 (57-82)	ARM-early and late ARM according to Bird's classification VA = 0.6	Color contrast sensitivity using computer graphics system	Significant elevation of threshold to identify tritan optotypes in ARM when compared with controls, and this was related to the severity of retinal changes.
Feigl et al (2005)[114]	Case-control	Case-13 Controls-13	63-77	Study eye-early ARM, defined as hard or soft distinct and indistinct drusen = 63 μm with or without RPE changes VA-6/6 to 6/12	Desaturated D-15 and Panel D-15	Pts with ARM demonstrated mainly tritan defects.

*Not available. ARM: Age-related maculopathy; CNV: Choroidal neovascularization; CV: Colour vision; Pt(s): Patient(s); Pig: Pigment; UL: Unilateral eye; VA: Visual acuity; Yrs: Years.

The CV defect may be the result of disruption of cone receptors or subsequent neuronal pathways by a disease process, and may be subclassified into congenital and acquired types. A type III blue–yellow defect (according to the classification proposed by Verriest[333]) is the most common type of acquired CV defect originating from macular pathology.

B. CHROMATIC FUNCTION AND AGE-RELATED MACULOPATHY

The details of 15 studies, which have investigated chromatic function in patients with ARM, are summarized in Table 5.[12,17,20,38–40,64,71,105,106,114,118,147,221,288] The data from all these studies, except two,[20,221] suggest that patients with early ARM have defective CV, with a tendency towards a tritan (blue–yellow) defect, and this is in full agreement with Kollner's rule that acquired macular diseases lead to disruption of blue–yellow color. Furthermore, these defects may worsen progressively with passage of time in patients who are at high risk of developing neovascular AMD.

Midena et al failed to demonstrate color discrimination abnormalities in 47 patients with ARM, and this observation is inconsistent with the majority of studies, which have investigated chromatic function in patients with ARM.[221] According to the investigators, one possible explanation for their finding may be that alterations of CV in early ARM were so subtle that the commercially available tests of CV that they employed were unable to detect them. Similarly, Atchison et al failed to observe a significant difference in color discrimination between patients with ARM and controls, but it is important to note that the definition of ARM used in that study included the presence of hard drusen and/or fine pigmentary changes, which probably represent normal aging changes.[20]

According to Bowman et al, color discrimination was observed to deteriorate with decreasing illuminance levels, and this effect was most marked in patients with ARM and least for the young normal control group.[39] Also, the deterioration in color discrimination with decreasing levels of illumination continues to accelerate along with increasing severity of tritan defects. Conversely, the defect in color discrimination decreases in severity with increasing illumination, and a level can be reached above which further improvement does not occur in spite of a further increase in illumination.

Furthermore, early ARM is associated with a significant decrease in the color-match area when compared with healthy subjects. Eisner et al, in two different studies, investigated the color-match area in the fellow eyes of patients with unilateral CNV in a cross sectional and prospective fashion.[105,106] The investigators demonstrated that these eyes were more likely to have a color-match area of magnitude zero or less when compared with age-matched controls. As the size of the color-match area relates to effective density of photopigment within the cone's outer segment, the presence of a smaller color-match area in patients with ARM may suggest a relative deficiency of existing photopigment in the cones.

Indeed, Elsner et al assessed color-matching measurements of long- and middle- wavelength-sensitive cones in 53 patients with early ARM, using a Maxwellian view color-matching device, and demonstrated that cone photopigment density was, on an average, less for patients with ARM when compared with normative data.[110] In addition, the color-matches of patients with early ARM differed from color-matches for normative data, in that more red primary or long wavelength color was required. The investigators suggested that a decreased ability of the cones to capture light may be attributable to an altered microenvironment, which reduces the quantal catch per cone, in eyes with ARM.

In addition, Eisner et al demonstrated that an abnormal color-match area was specific, as well as highly sensitive (in combination with the DA time constant), for high-risk eyes with ARM, by demonstrating such abnormalities in fellow eyes of patients with unilateral neovascular AMD.[106] This observation is consistent with that of Smith et al, where an increase in morphological changes (according to Sarks classification) in patients with ARM was associated with more severe abnormalities of color-matching.[288] Lastly, the effect of stimulus area on the colour match, in combination with slow foveal DA, was the most effective combination of visual function parameters for identification of eyes which went on to develop CNV over a follow-up period for at least 18 months.[105]

Tests of color CS sensitivity use isoluminant color stimuli of varying contrast to allow separation of a luminance defect from a chromatic defect,[147] and in these tests, color contrast thresholds are determined along the protan, deutan, and tritan color confusion axes. Three studies have investigated color CS in patients with ARM using a computer graphics system developed by Arden et al,[14,15] and data from all these studies have consistently demonstrated an increase in threshold along the tritan axis.[17,118,147] Furthermore, this increase in tritan threshold was related to the severity of morphological retinal changes in ARM,[17] and worsened progressively in patients who developed advanced ARM over a 2-year period of follow-up.[147]

It has been suggested that discrimination in color saturation is affected earlier in the ARM process than is hue discrimination, and therefore CV tests which

evaluate color discrimination at reduced saturation may be relatively more effective for detection of CV defects in early ARM. Indeed, the desaturated D-15 test, which assess color discrimination at reduced saturation, is more sensitive to functional loss in ARM than the panel D-15 test, and may be used to quantify a CV defect in early ARM.[40] However, there is a high rate of false positives in discriminating between early ARM and normal subjects when using the desaturated D-15 test,[64] probably because of the age-related decline in blue–yellow sensitivity.[103]

Of the three cone systems, the S-cones seem to be most vulnerable to damage in ARM. Although the reason for this observation remains unclear, various possibilities have been hypothesized. First, the S-cone pathway is intrinsically prone to damage because of its territorial nature (the receptive fields of S-cones do not overlap), and therefore damage to a single S bipolar/ganglion cell would result in a corresponding area of scotoma.[41] Second, although the SW sensitive pathway is affected to the same extent as the other cone pathways, psychophysical losses related to SW sensitive pathways might appear exceptionally pronounced due to the unique nature of the S-cone neuronal connections.[147] According to Hood et al, SWS pathways have a more limited response range than that of other cone pathways.[148] Therefore, SWS pathways have a larger disease-related change in threshold when compared with other cone pathways, and, consequently, an apparent vulnerability to retinal disease. Third, S-cones may be more susceptible to alterations in the metabolic environment of the RPE-photoreceptor complex, such as photopigment turnover, due to an increase in the diffusion distance, than other cone systems.[292] Lastly, the SW sensitive pathway may be selectively damaged during the pathogenesis of ARM, similar to other eye diseases such as glaucoma, and this may be attributable to relatively lower levels of MP in patients predisposed to ARM.[147] Indeed, Haegerstrom-Portnoy et al observed a relative preservation of S-cone sensitivity at the fovea, where the density of MP is highest, than at the parafovea, in elderly subjects.[133] It is possible that high MP optical density results in reduced S-cone stimulation, which ultimately may lead to a compensatory gain in the response to S-cone stimulation. Furthermore, Hammond et al demonstrated that elderly subjects with high MP optical density have higher S-cone sensitivity when compared with age-matched subjects with lower MP density.[138] As ARM seems to represent a gradual transition from aging to degenerative changes, these observations may suggest a role for MP in preserving S-cone sensitivity, and possibly in preventing the development of ARM.

In addition, several investigators have specifically measured S-cone sensitivity and compared it with other cone mechanisms in patients with early ARM. Eisner et al investigated S-cone sensitivity in the fellow eyes of patients with CNV, and demonstrated significantly lower S-cone sensitivity when compared with age-matched controls.[104] This observation was consistent with that of Haegerstrom-Portnoy et al, where lower S-cone sensitivity was observed in patients with ARM when compared with pre ARM patients and with normal elderly subjects.[135] Furthermore, Eisner et al, in three different studies, demonstrated that lower S-cone sensitivity was associated with high-risk features (defined in terms of large confluent drusen and pigmentary changes), and with the subsequent development of CNV in fellow eyes of patients with unilateral CNV in a longitudinal study.[101,105,106] Similarly, Sunness et al demonstrated lower S-cone sensitivity in association with high-risk drusen characteristics (soft confluent drusen and/or focal hyperpigmentation), although the association was weak.[305]

In conclusion, patients with early ARM have an acquired CV defect, which is generally recognized as a blue–yellow (tritan) defect, and these defects tend to worsen progressively in patients who are at increased risk for developing advanced disease. Furthermore, an abnormal color-match area, in combination with prolonged DA time constant, may identify eyes at risk for developing neovascular AMD with good degree of sensitivity and specificity. Lastly, lower S-cone sensitivity may act as a potential marker for the ultimate development of neovascular AMD.

XI. Correlation Between Histopathologic Changes and Psychophysical Function

Age-related maculopathy is a heterogeneous group of disorders that affects the RPE, Bruch's membrane, and choriocapillaris (the RPE/Bruch's membrane complex), and involves pathological changes superimposed on the aging process.[126,271] The earliest histopathologic feature of ARM is the accumulation of abnormal material within Bruch's membrane, which may be in the form of discrete or diffuse deposits.[127,271]

The abnormal material within Bruch's membrane, if rich in neutral lipids, creates a hydrophobic barrier that impairs the metabolism, and subsequently function, of the photoreceptors.[242] The reason is that the outer retina, including the photoreceptors, is supplied by the choroidal circulation, and, therefore all nutrients to, and metabolites from, the RPE and photoreceptors must cross Bruch's membrane. Although dysfunction occurs in both rods and cones, rods typically are affected

earlier than are cones. According to Curcio et al, such preferential loss of rods over cones has been histopathologically observed in three of four eyes examined with early ARM.[85]

Psychophysical studies have supported the histopathological evidence of preferential loss of rods over cones in patients with early ARM. According to Jackson et al, 87% of patients with early ARM demonstrated a greater magnitude of decline in the mean scotopic RS when compared with mean photopic RS.[153] In addition, a delay in the rod-mediated portion of the DA curve was significantly greater when compared with the cone-mediated portion. Furthermore, Leibrock and co investigators, in a theoretical model of DA, proposed that slow rod-mediated recovery might indicate a limited availability of the 11-*cis*-retinal to rod photoreceptors.[197] Indeed, the barrier function induced by the thickened Bruch's membrane may result in reduced retinoid transfer from blood to the RPE, which in turn leads to a localized scarcity of 11-*cis*-retinal, and, therefore, prolonged DA in patients with ARM.

Alternatively, thickening of the Bruch's membrane may alter the metabolism of the photoreceptors, therefore result in functional changes, by altering the choroidal circulation. There is circumstantial evidence that diffusible substances, which are produced by the RPE, modulate structure and function of the choroid.[11,122,172] The diffusion barrier, created by a thickened Bruch's membrane, prevents these agents from diffusing towards the choroid, and may cause the choroidal capillaries to change from a sinusoidal system to a tubular arrangement.[233] Consequently, there may be delayed and prolonged choroidal filling, evident on fluorescein angiography. Indeed, Chen et al demonstrated discrete areas of decreased scotopic RS in seven of eight eyes, with fluorescein angiographic evidence of prolonged choroidal filling.[63] However, no such areas of decreased retinal sensitivity, compared with the background sensitivity, were observed in eyes without delayed choroidal perfusion.

With increasing deposits within the Bruch's membrane, there is disruption of functional channels within the RPE/Bruch's membrane complex, leading to gradual death of the photoreceptor cells in GA. Worsening of various psychophysical functions over time in ARM patients may possibly reflect such functional disruption of the photoreceptor cells. The late stage of GA is associated with gradual loss of cone photoreceptors at the fovea, and when the number of cone loss exceeds the Nyquist limit, a clinically evident deterioration in spatial VA occurs.

In summary, histopathological and psychophysical studies have consistently demonstrated that photoreceptor degeneration and loss occurs before the disease in the RPE/Bruch's membrane complex progresses to advanced ARM.

XII. Discussion

In this review article, we have critically appraised the evidence for subtle deficits in psychophysical function, such as spatial and temporal vision, adaptation mechanisms, VF sensitivity, chromatic function, in the prodromal phases of ARM. We have found consistent evidence of deficits in many of the complex psychophysical measures of the physiological status of the photoreceptors and of the RPE. These visual functions are affected early in the disease process of ARM before high contrast VA is reduced, and before morphological changes in the fundus are apparent clinically.

Some of these psychophysical tests often correlate with subjective and relatively undefined symptoms of patients with early ARM, and may reflect an individual's limitation in terms of vision-dependent activities required for normal daily livings. Patients with early ARM often experience difficulty in changing light illumination, and this may be attributable to altered adaptation mechanisms in the photoreceptor cells, such as DA and glare recovery, in the early stages of disease. In addition, difficulty in night driving, frequently reported by ARM patients, has been related to reduced scotopic sensitivity, and supports the hypothesis that dysfunction in rod photoreceptors occur early in the disease process.

The disturbance in psychophysical function is not limited to the macular region, but extends well into the retinal periphery, beyond the ophthalmoscopically visible lesions of ARM. According to the cited studies, visual dysfunction extends 25 degrees from the fovea for rod adaptation, 40 degrees for cone adaptation, 20 degrees for temporal function, and 8 degrees for CS. This suggests that there is a global impairment of retinal function in patients with ARM, and this observation is in full agreement with the electrophysiological measures of rod and cone mediated functions in ARM.

Furthermore, this review article demonstrates that there is an alteration of various cone-mediated visual functions (such as color vision, temporal function, and S-cone sensitivity) in patients with early ARM. This suggests that dysfunction of cone photoreceptors may occur, in combination with rod dysfunction, in the early stages of ARM despite unaltered foveal cone numbers as evident in histopathological studies. The widespread dysfunction of the cone photoreceptors in early ARM may reflect either a barrier effect of Bruch's membrane or dysfunction in the RPE. Alternatively, the cone dysfunction may

arise from lower optical density and/or reduced quantal catch of the photopigment.

The majority of the cited studies in this review article are cross-sectional in nature and, therefore, there is paucity of longitudinal evidence in support of a diagnostic and prognostic role for psychophysical testing in ARM. Nevertheless, of the ten studies that have investigated longitudinal changes in psychophysical function (either alone or in combination) in ARM, eight have demonstrated worsening of S-cone sensitivity, absolute DA foveal sensitivity, PSRT, DA in combination with color-match area effect, flicker sensitivity, and mesopic VF defects in association with progression of ARM over time, suggesting that these parameters of psychophysical function may act as potential markers for the ultimate development of neovascular AMD.[12,101,105,129,147,215,268,306]

It is worth noting that the majority of the cited studies have investigated only small subgroups of ARM patients, and the reports lack consistency in terms of grading and classification of ARM, and in terms of methodology. Also, the age-related decline in psychophysical function must be kept in mind when interpreting the results from such studies, because not all studies have compared the results from patients with ARM to age-matched controls. These factors may possibly explain some of the inconsistencies among the results from various studies investigating psychophysical function in patients with ARM.

Furthermore, some of the psychophysical tests in the cited studies (flicker sensitivity, foveal DA sensitivity, and color-match area) are difficult to perform in a typical clinical setting and in clinical trials, as the tests are time consuming and require significant expertise, and typically employ expensive and sophisticated equipment. Lastly, good comprehension and an ability to concentrate are essential for meaningful psychophysical testing, and therefore some ARM patients with declining cognitive functions, along with other associated sensory deficits, may not perform these tests to an optimum level.

Nevertheless, based on the studies reviewed in this article, the authors suggest that the following parameters of psychophysical function in early ARM, alone or in combination, may be helpful in identifying eyes at high risk of developing neovascular AMD, with a reasonable degree of sensitivity and specificity: S-cone sensitivity; flicker sensitivity; DA (including absolute foveal sensitivity); color-match area; PSRT.

XIII. Conclusion and Future Directions

Based on this review article, it is clear that several aspects of visual function are adversely affected in early ARM, before a change in distance visual acuity is detectable. In addition, psychophysical function has been linked with high-risk features and subsequent development of neovascular AMD, suggesting that some of these functions (such as S-cone sensitivity, flicker sensitivity, DA, color-match area, and PSRT) may be of prognostic value in identifying eyes at risk for developing visually consequential disease. However, the existing psychophysical tests are time-consuming, require significant expertise, expensive and sophisticated equipment, and therefore are not applicable in clinical practice. Furthermore, the diagnostic and prognostic value of these psychophysical parameters of vision has yet to be tested in a randomized, prospective and controlled fashion. We need, and should support, studies designed to assess whether psychophysical changes before the onset of visually consequential ARM are of clinical or of prognostic value.

XIV. Method of Literature Search

References for this review article were identified through a systematic search of the Medline database using PubMed Web site (1959 to 2007). Further articles, abstracts, and textbook references, generated from reviewing the bibliographies of the initial search, were retrieved and included. Additional sources (such as non-peer reviewed articles, Web sites, and book chapters) were included based on the relevance to subject; however, such material was cited in the text rather than in the reference list. All articles read were in English, and when articles in other languages were of relevance, their abstracts in English were read. The following key words and combinations of these words were used in compiling the initial search: *age-related macular degeneration; age-related maculopathy; visual acuity; low-contrast visual acuity; hyperacuity; contrast sensitivity; temporal function; flicker sensitivity; dark adaptation; photostress test; perimetry; preferred retinal locus; reading speed; colour vision; short wavelength cone; macular pigment; visual function; psychophysical function.*

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Outline

I. Introduction
II. Anatomy of the macula
III. Age-related maculopathy: definition
IV. Age-related maculopathy: why the macula?
V. Visual psychophysics
VI. Spatial vision in ARM
  A. Visual acuity
    1. Definition and basic principle
    2. Visual acuity and ARM
      a. Visual acuity, luminance, and ARM
      b. Visual acuity, quality of life, and ARM
  B. Low contrast visual acuity
  C. Hyperacuity
  D. Reading speed
    1. Definition and basic principle
    2. Reading speed and ARM
      a. Reading speed, illumination, and ARM
      b. Reading speed, preferred retinal locus and cortical adaptation, and ARM
      c. Reading speed, rehabilitation, and ARM
  E. Contrast sensitivity
    1. Definition and basic principle
    2. Contrast sensitivity and ARM
VII. Temporal visual function in ARM
  A. Temporal resolution
  B. Temporal contrast sensitivity
VIII. Visual adaptation in ARM
  A. Dark adaptation
    1. Definition and basic principle
    2. Dark adaptation and ARM
  B. The photostress test
    1. Definition and basic principle
    2. The photostress test and ARM
IX. Perimetry
  A. Definition and basic principle
  B. Visual fields and ARM
X. Color vision
  A. Definition and basic principle
  B. Chromatic function and ARM
XI. Correlation between histopathological changes and psychophysical function
XII. Discussion
XIII. Conclusion and future direction
XIV. Method of literature search