Detection of Age-Related Macular Degeneration Using a Nonmydriatic Digital Camera and a Standard Film Fundus Camera

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Objective: To compare gradings of lesions associated with age-related macular degeneration (AMD) from digital and stereoscopic film images.

Design: Instrument validation study.

Participants: Sixty-two subjects (124 eyes) with varying degrees of AMD, including no AMD.

Methods: Images of the optic disc and macula were taken using a 45° digital camera (6.3 megapixels) through dark-adapted pupils and pharmacologically dilated pupils. In addition, 30° stereoscopic retinal film images were taken through pharmacologically dilated pupils of the same eyes. All images were graded for drusen size, type, and area; pigmentary abnormalities; geographic atrophy; and neovascular lesions using the modified Wisconsin Age-Related Maculopathy Grading System. Exact agreement and unweighted $\kappa$ scores were calculated for paired gradings resulting from digital and film images.

Main Outcome Measure: Agreement between gradings obtained from stereoscopic slide transparencies and digital nonstereoscopic images.

Results: Exact agreement between gradings of digital and stereoscopic film images taken through pharmacologically dilated pupils was 91% ($\kappa=0.85$) for the categories of none, early AMD, and late AMD. Exact agreement for gradings of digital images taken through dark-adapted pupils compared with gradings of film images was 80% ($\kappa=0.69$). Exact agreement for gradings of digital images captured through dark-adapted and pharmacologically dilated pupils was 86% ($\kappa=0.78$). In addition, $\kappa$ scores for agreement between different approaches for individual lesions were moderate to almost perfect.

Conclusions: Gradings resulting from high-resolution digital images, especially when the pupil is pharmacologically dilated, are comparable with those resulting from film-based images. We conclude that digital imaging of the retina is useful for epidemiological studies of AMD.

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GE-RELATED MACULAR DEGENERATION (AMD) is a major cause of visual impairment.1,2 Fundus photography with film-based cameras has routinely been used to document the presence and severity of AMD in clinical practice and epidemiological studies.3-5 Optimally, fundus photography is performed through a pharmacologically dilated pupil. However, in situations in which mydriatic agents cannot be used, photography with film-based nonmydriatic cameras has successfully been used as an alternative means of imaging for AMD.6-7

Recently, new high-resolution digital cameras have become available and are being used to detect AMD in research and clinical settings.6,8 The purpose of this article is to compare the severity of AMD using images of the same retinas recorded with 3 different imaging systems: nonstereoscopic color 45° retinal images taken with a digital camera through a dark-adapted pupil, nonstereoscopic color 45° retinal images taken with a digital camera through a pharmacologically dilated pupil, and stereoscopic color 30° retinal images taken with a standard film camera through a pharmacologically dilated pupil. In addition, patient acceptance of these imaging systems was compared.

METHODS

SUBJECTS

Our study included 62 patients seen at the University of Wisconsin Retina Clinic (Madison). We attempted to recruit at least 30 patients with a diagnosis of AMD. Tenets of the Declaration of Helsinki were followed, and approval from the institutional human experimentation committee was granted. Informed
consent was obtained from each participant. Birth dates and history of cataract, cataract surgery, diabetes, AMD, and retinal photocoagulation were ascertained in 58 subjects (4 patients did not provide a history).

PHOTOGRAPHY

Participants were seated in a darkened room. Pupil size was estimated by comparing it to progressively increasing circles from 1 to 9 mm in diameter. Both eyes of each participant were photographed in a similar fashion using a 45° 6.3-megapixel digital nonmydriatic camera (Canon, Lake Success, NY). This camera used an infrared light to televise a view of the fundus through a dark-adapted pupil. Field location and focusing of the retinal image were accomplished by the photographer's use of a laptop computer. Two photographic fields were taken of each eye, the first centered on the optic disc and the second centered on the fovea (Figure). The 45° image was mimified ×0.64 (at 0 diopters) compared with that taken with a standard 30° camera (Zeiss FF4; Carl Zeiss, Inc, Jena, Germany) (Figure). The iris color was determined by direct observation and was recorded as gray/blue, yellow/green, or tan/brown. The presence of any corneal or lens opacity was recorded. The photographer recorded the lengths of time necessary for pupil dilation and fundus photography.

One drop of 2.5% phenylephrine hydrochloride and 1 drop of 1% tropicamide were then instilled in the cul-de-sac of each eye to obtain dilation. The size of the dilated pupil was estimated. Two images of the same retinal fields, as described previously, were taken with the nonmydriatic digital camera through the pharmacologically dilated pupil.

Stereoscopic retinal photographs were taken with a standard 30° fundus camera (Zeiss FF4) centered on the disc (Diabetic Retinopathy Study11 standard field 1) and macula (standard field 2), and a nonstereoscopic color fundus photograph was taken temporal to but including the fovea of each eye.12,13 The times at the beginning and end of photography were recorded. Subjects were asked to evaluate their comfort with the flash of each camera on a 10-step scale ranging from 1 (no discomfort) to 10 (extremely uncomfortable) after each set of photographs. At the end of the photography session, participants were asked the following question: “Which is least tolerable: having your pupils dilated, the flash, both the same, or both tolerable?”

GRADING

The digital images were graded using the standard AMD protocol. Graders were masked with respect to information about the subject. Digital images of both eyes were graded by the same grader; the right and left eyes from the same photography session of each participant were both displayed to the grader. Graders were asked to judge field definition, focus of the photographs, pupil size, and the appearance of artifacts prior to determining AMD severity level. Each image was graded twice (a preliminary and a detail grade) online using the Multi-Ethnic Study of Atherosclerosis protocol,14 a modification of the Wisconsin Age-Related Maculopathy Grading System.13 Every digitized image was graded twice by the same grader for the preliminary grading. For the first grading, there was no image manipulation except magnification (no contrast enhancement, lightening, or red-free images). For the second grading, the full complement of image enhancement tools was available.

If the preliminary and detail gradings agreed, the grading was considered final. If there was disagreement between gradings for a lesion, the image was sent to an edit grader for re-evaluation of that lesion without knowing what the specific disagreement was. The preliminary, detail, and edit gradings were compared again for agreement. If the edit grading agreed with either the preliminary or detail grading, that one was considered final. If a disagreement remained, the grading of the image was adjudicated by the Reading Center codirector (R.K.). Nine different graders were assigned to perform either preliminary, detail, or edit gradings for each image. No grader saw the same eye twice.

All stereoscopic photographs taken with the film-based 30° camera used color 35-mm slide film (Ektachrome 100 Plus Professional; Kodak, Rochester, NY), which was processed and returned as 2 × 2-in slides. The slides were mounted in clear plastic mounting sheets and graded using a light box and a Donaldson stereo viewer with original magnification ×5. Two gradings for AMD were performed for each eye.12 First, a preliminary masked grading was done by one senior grader for drusen size, type, and area; pigmentary abnormalities; geographic atrophy; and exudative lesions. Next, detailed gradings were performed by other experienced graders. For detailed grading, each eye was graded independently of the fellow eye. The assessment consisted of a subfield-by-subfield, lesion-by-lesion evaluation of each photo-
graph set using the Wisconsin Age-Related Maculopathy Grading System.\textsuperscript{13,15} Then a series of edits and reviews was performed similar to that done in the digital grading. The presence and severity of specific lesions (eg, maximum drusen size, type, and area and pigmented abnormalities), as determined by detailed grading, were compared with those of the preliminary grading. Standardized edit rules were used to adjudicate disagreements.\textsuperscript{13,15}

DEFINITIONS

Early AMD was defined as the presence of soft indistinct drusen only or either hard or soft drusen and pigmentary abnormalities (increased retinal pigment or retinal pigment epithelial [RPE] depigmentation) in the absence of signs of geographic atrophy or exudative lesions. Late AMD was defined as the presence of either geographic atrophy or signs of exudative macular degeneration.

STATISTICAL ANALYSIS

Differences between means were tested for statistical significance using the $t$ test or, in the case of more than 2 groups, analysis of variance. Agreement between grading methods was evaluated with the $\kappa$ statistic.\textsuperscript{16,17}

RESULTS

The 62 participants ranged in age from 30 to 90 years; the median age was 64 years. Twenty-six (45%) of 58 had a history of cataract, and 10 (17%) of 58 had a history of cataract surgery. Of the 116 irises, 68 (59%) were judged to be gray/blue, 14 (12%) yellow/green, and 34 (29%) tan/brown. We photographed 101 eyes through dark-adapted and pharmacologically dilated pupils using the digital camera and through pharmacologically dilated pupils with the film camera. Twenty-three eyes were not graded because of non-AMD processes (such as pigmentary dystrophies) or photocoagulation scars. There was no significant difference regarding participants' ability to tolerate the different types of photography (data not shown).

Table 1 lists comparisons of AMD severity by grading of manipulated images taken with a nonmydriatic 45° digital camera through both dark-adapted and pharmacologically dilated pupils as well as stereoscopic film images taken through pharmacologically dilated pupils. When categorizing AMD as none, early, or late, agreement was better between digital and film images taken through pharmacologically dilated than dark-adapted pupils ($P=.03$). Without pharmacological dilation, more digital than film images were ungradable for AMD severity level. Exact agreement between digital images of dark-adapted eyes and those taken after pharmacological dilation for AMD severity level was 86.1% ($\kappa=0.78$; SE=0.05) (Table 1).

Exact agreement for specific AMD lesions was high with moderate to almost perfect $\kappa$ scores (Table 2). When disagreements were present for specific AMD lesions, drusen 125 µm in diameter or greater were more likely to be graded as present (10.9% vs 2.0%) and increased retinal pigment (3.0% vs 5.0%), RPE depigmentation (1.0% vs 5.0%), and RPE detachment (1.0% vs 5.9%) were less likely to be graded as present in manipulated digital images of dark-adapted pupils compared with film images of pharmacologically dilated pupils. Drusen 125 µm in diameter or greater were more likely to be graded as present (5.9% vs 2.0%) but RPE depigmentation (4.0% vs 5.9%) and RPE detachment (2.0% vs 5.9%) were less likely to be graded as present in manipulated digital images compared with film images of pharmacologically dilated pupils.

The mean±SD score on the comfort scale varied from 2.4±0.8 (1 being the most comfortable and 10 the least comfortable) to 4.5±0.7 (10 being the most uncomfortable and 1 being the least uncomfortable) for the digital camera. The mean±SD score varied from 2.6±0.8 (1 being the most comfortable and 10 the least comfortable) to 4.6±0.7 (10 being the most uncomfortable and 1 being the least uncomfortable) for the film camera.

The mean±SD score on subjective comfort was 5.0±0.6 (1 being most uncomfortable and 10 being most comfortable) with 23 eyes being graded for subjective comfort. The mean±SD score was 4.9±0.7 (1 being most uncomfortable and 10 being most comfortable) with 9 eyes being graded for subjective comfort.

Abbreviation: ARM, age-related macular degeneration.

*For dark-adapted eyes photographed with a nonmydriatic 45° digital camera vs a standard 30° film camera, exact agreement was 80.2% ($\kappa=0.69$; SE=0.06). For dark-adapted eyes vs pharmacologically dilated eyes photographed with a nonmydriatic 45° digital camera, exact agreement was 86.1% ($\kappa=0.78$; SE=0.05). For pharmacologically dilated eyes photographed with a nonmydriatic 45° digital camera vs a standard 30° film camera, exact agreement was 91.1% ($\kappa=0.85$; SE=0.05).

### Table 1. Comparison of Severity of Age-Related Macular Degeneration by Gradings of Photographs Taken With a Nonmydriatic Digital 45° Camera and Standard 30° Film Camera

<table>
<thead>
<tr>
<th>Pharmacologically Dilated Eyes</th>
<th>Color Stereoscopic 30° Film Camera</th>
<th>Nonmydriatic Digital 45° Camera</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonmydriatic 45° digital camera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dark-adapted eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ARM</td>
<td>46 1 0 48</td>
<td>47 1 0 0 48</td>
</tr>
<tr>
<td>Early ARM</td>
<td>6 9 4 19</td>
<td>3 13 3 0 19</td>
</tr>
<tr>
<td>Late ARM</td>
<td>0 1 24 0</td>
<td>0 25 0 0 25</td>
</tr>
<tr>
<td>Cannot grade</td>
<td>5 2 0 9</td>
<td>4 3 0 2 9</td>
</tr>
<tr>
<td>Total</td>
<td>57 13 28 3 101</td>
<td>54 17 28 2 101</td>
</tr>
<tr>
<td>Pharmacologically dilated eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ARM</td>
<td>52 0 0 2 54</td>
<td></td>
</tr>
<tr>
<td>Early ARM</td>
<td>4 12 1 0 17</td>
<td></td>
</tr>
<tr>
<td>Late ARM</td>
<td>0 1 27 0 28</td>
<td></td>
</tr>
<tr>
<td>Cannot grade</td>
<td>1 0 0 1 2</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>57 13 28 3 101</td>
<td>54 17 28 2 101</td>
</tr>
</tbody>
</table>

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comfortable) for digital photography through dark-adapted pupils to 2.3 ± 2.0 for digital photography and 3.9 ± 2.6 for film-based photography through pharmacologically dilated pupils. The differences among these means were statistically significant (P < .001). Persons with brown or green eyes were more likely to give higher scores for discomfort (P = .01) than gray- or blue-eyed persons. There was no effect of age or pupil size on comfort with digital or film photography (data not shown).

Our study demonstrated some of the strengths and limitations of both the nonmydriatic digital 45° camera and the standard 30° film-based camera. The advantages of the nonmydriatic digital 45° camera in contrast to the standard 30° film-based camera were that it (1) was less expensive; (2) took a shorter time to learn to use; (3) provided excellent resolution and images that could be edited and adjudicated gradings using higher-resolution images (3072 × 2048 pixels). The nonstereoscopic digital images may have contributed to the grader’s missing retinal abnormalities such as RPE depigmentation that are seen more easily on stereoscopic images. The findings in our study are consistent with another study that compared gradings of stereoscopic digital images and film-based images taken through a pharmacologically dilated pupil. In that study, the κ value for the between-technique agreement for stages of AMD severity was approximately 0.76. The lower level of agreement in that study compared with ours may have been because AMD severity levels were based on unedited and unadjudicated gradings of low-resolution (800 × 600 pixels) images, whereas our results were based on edited and adjudicated gradings using higher-resolution images (3072 × 2048 pixels).

In our study, there was a higher frequency of larger (≥125 µm in diameter) soft drusen and a lower frequency of increased retinal pigmentation and RPE depigmentation on nonmydriatic digital images than film images. These differences were more marked for images taken through dark-adapted than pharmacologically dilated pupils, and they were not found in another study when gradings of stereoscopic digital images were compared with those from stereoscopic film-based images (R. van Leeuwen, MD, PhD, written communication, January 2004). We speculate that a lack of stereoscopic effect may have led to a poorer ability to distinguish the edges of large drusen or detect subtle RPE depigmentation, especially when the contrast was poor. However, this did not greatly affect the agreement between gradings using the 2 photography approaches for detecting AMD severity in our study. The decreased ability to detect pigmentary abnormalities with digital photography was consistent with findings from a recent study examining the agreement between gradings of digitized images that were made from film-based images using the original film slides. In that study, agreement was good for detecting RPE depigmentation but poor for detecting increased retinal pigmen-

### Table 2. Percentage of Eyes With Agreement Between Gradings and Specific Lesions Caused by Age-Related Macular Degeneration*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Digital (OA vs Digital (PD))</th>
<th>Digital (OA vs Film)</th>
<th>Digital (PD) vs Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drusen size &gt; 125 µm in diameter</td>
<td>Exact Agreement, %</td>
<td>% Present†</td>
<td>κ (SE)</td>
</tr>
<tr>
<td>Soft distinct drusen§</td>
<td>84.2</td>
<td>37.6</td>
<td>0.71 (0.06)</td>
</tr>
<tr>
<td>Drusen area &gt; 500 µm in diameter</td>
<td>82.2</td>
<td>22.8</td>
<td>0.64 (0.07)</td>
</tr>
<tr>
<td>Increased retinal pigmentation§</td>
<td>85.2</td>
<td>31.7</td>
<td>0.71 (0.06)</td>
</tr>
<tr>
<td>RPE depigmentation§</td>
<td>79.2</td>
<td>21.8</td>
<td>0.50 (0.09)</td>
</tr>
<tr>
<td>RPE detachment§</td>
<td>89.1</td>
<td>16.8</td>
<td>0.69 (0.08)</td>
</tr>
<tr>
<td>Exudative§</td>
<td>90.1</td>
<td>22.8</td>
<td>0.75 (0.07)</td>
</tr>
<tr>
<td>Geographic atrophy§</td>
<td>87.1</td>
<td>16.8</td>
<td>0.61 (0.10)</td>
</tr>
</tbody>
</table>

Abbreviations: DA, dark adapted; PD, pharmacologically dilated; RPE, retinal pigment epithelial.

* For all comparisons, the sample size was 101.
† In digital (PD) images.
‡ In film images.
§ Present vs absent.
This might have resulted from a lack of capturing pigment in scanning the film image. It is also possible that differences in spectral sensitivity between film and digital imaging contribute to this discrepancy.

Digital photography provides the grader with powerful tools to examine poor-quality images. For example, without pharmacological dilation, the small pupil may lead to relatively dark images that might obscure AMD lesions. In some cases, manipulating the brightness in such images provides easier detection of these lesions. We had expected that for AMD lesions, manipulated digital images would be more closely correlated with film images than unmanipulated digital images. However, we did not find this to be the case (R.K., unpublished data, 2004). Caution must be exercised when manipulating digital images to avoid the introduction of artifacts that might result in false-positive or false-negative results. For this reason, we have developed protocols that specify allowable manipulations of magnification, contrast, and brightness as well as use of specific color channels with the digital images. The findings from the manipulated images must be seen on the original unmanipulated images for the lesions to be graded as present.

The appropriateness of using the digital nonmydriatic camera in epidemiological studies of AMD depends on the objectives of the specific study. When feasible, stereoscopic fundus photography taken with a digital or film camera through pharmacologically dilated pupils is the preferred approach for detecting AMD. If possible, an ongoing epidemiological study or clinical trial should not change from film to digital capture of retinal images. However, if AMD is not the primary endpoint in a new study and pharmacological dilation of the pupils is not feasible, digital photography using a nonmydriatic camera should provide an alternative to stereoscopic fundus film photography. Furthermore, the nonmydriatic digital camera offers a distinct advantage compared with the nonmydriatic film camera because it enables the photographer to take another image of the retina when the first image is poor or ungradable owing to blinking or other artifacts. Because of its lower flash intensity, the nonmydriatic digital camera allows photography of 2 or more fields of both eyes in a relatively short time compared with the nonmydriatic film camera.

In summary, data from our study show moderate to almost perfect agreement between gradings of AMD severity from digital and film-based images. The use of digital photography in epidemiological studies has resulted in the development of new protocols and software for the capture, transmission, and reading of digital images. New software has enabled application of the Wisconsin Age-Related Maculopathy Grading System currently used in grading film images. Further standardization and development of guidelines for using, taking, and grading digital images are necessary to allow comparisons of results among different systems. This will be especially important in multicenter studies using different digital cameras and software to capture images.

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