The Microperimetry of Resolved Cotton-Wool Spots in Eyes of Patients With Hypertension and Diabetes Mellitus

Jae Suk Kim, MD; Anjali S. Maheshwary, MD; Dirk-Uwe G. Bartsch, PhD; Lingyun Cheng, MD; Maria Laura Gomez, MD; Kathrin Hartmann, MD; William R. Freeman, MD

Background: Retinal cotton-wool spots (CWSs) are an important manifestation of retinovascular disease in hypertension (HTN) and diabetes mellitus (DM). Conventional automated perimetry data have suggested relative scotomas in resolved CWSs; however, this has not been well delineated using microperimetry. This study evaluates the retinal sensitivity in documented resolved CWSs using microperimetry.

Methods: Retinal CWSs that resolved after 10 to 119 months (median, 51 months) and normal control areas were photographed to document baseline lesions. Eye-tracking, image-stabilized microperimetry with simultaneous scanning laser ophthalmoscopy was performed over resolved CWSs, adjacent uninvolved areas near the lesion, and in location-matched normal patients (age-matched).

Results: A total of 16 eyes in patients with DM or HTN (34 resolved CWSs) and 16 normal control eyes (34 areas) were imaged. The mean (SD) sensitivity of resolved CWSs in the eyes of patients with HTN and DM was 11.67 (3.88) dB and 7.21 (5.48) dB, respectively. For adjacent control areas in the eyes of patients with HTN and DM, the mean (SD) sensitivity was 14.00 (2.89) dB and 11.80 (3.45) dB, respectively. Retinal sensitivity was significantly lower in areas of resolved CWSs than in the surrounding controls for patients with HTN ($P = .01$) and those with DM ($P < .001$). Scotomas in patients with DM were denser than those of patients with HTN ($P < .05$).

Conclusions: Cotton-wool spots in patients with DM and HTN leave permanent relative scotomas detected by microperimetry. Scotomas are denser in eyes of patients with DM than in those with HTN. In addition, among patients with DM, adjacent retinas not involved with CWSs have lower retinal sensitivity than in age-matched controls.

Arch Ophthalmol. 2011;129(7):879-884

THE COTTON-WOOL SPOT (CWS) is a commonly encountered retinal lesion. These yellowish white areas are associated with multiple disease processes but are most commonly found in patients with diabetes mellitus (DM) and hypertension (HTN). Although controversial, the CWS has been shown to be a localized accumulation of axoplasmic debris found in the retinal nerve fiber layer. This debris results from interruptions of organelle transport in ganglion cell axons. There are many factors that can cause focal interruption of axonal flow; however, clinically the commonest cause is ischemia. An alternative theory suggests that CWSs are merely sentinels of retinal nerve fiber layer disease. Clinically, CWSs disappear in 4 to 12 weeks and for the most part are asymptomatic. However, there have been reports that describe the development of scotomas at the site of these resolved CWSs as well as studies that suggest that signal transmission failures occur in the ganglion cell axons that pass through these regions.

Previously, our group has shown that an acute CWS on time-domain and spectral-domain optical coherence tomography (OCT) is hyperreflective in the inner retina with a dramatically increased average decibel reflectivity. As the lesions resolve, a slightly hyperreflective nodular area can be identified at the sites of the lesions for up to 3 months from the time they were identified. With time, the reflectivity of the inner retina in the area of the CWS become closer to normal. The CWS-induced destruction of the nerve fiber layer leads to a small focal defect in the area of the CWS as well as damages the axons of the more peripheral ganglion cells. This can result in an additional, more diffuse defect in retinal sensitivity.

Author Affiliations:
Departments of Ophthalmology, Jacobs Retina Center at Shiley Eye Center, University of California, San Diego, La Jolla (Drs Kim, Maheshwary, Bartsch, Cheng, Gomez, Hartmann, and Freeman), and Sanggye Paik Hospital, Inje University, Seoul, South Korea (Dr Kim).
Microperimetry has become a common way to measure macular function and assess the natural history and treatment outcome in macular disease. Microperimetry incorporates an eye tracker, allows automated follow-up examination at the same retinal loci, and is combined with a color fundus camera for image registration. It has become an important tool in gathering data about retinal function in patients with a variety of diseases.

Our purpose in this study was to evaluate retinal sensitivity using microperimetry after documented CWS regression in patients with HTN or DM. Since it has been shown that permanent structural changes can be imaged with OCT after resolution of these lesions, it seems logical that retinal function, as might be measured by microperimetric sensitivity, may be abnormal as well. Detection of retinal damage from these lesions may allow understanding of why patients with a seemingly normal fundus examination have persistent scotomas and decreased acuity in 2 commonly encountered diseases.

This study evaluated 12 patients identified as having CWSs from 1999 through 2009. Six of the patients had HTN, and 6 of the patients had DM. One of the patients had both HTN and DM, but fluorescein angiography changes were predominantly diabetic; thus, this patient was classified as having a diabetic CWS. None of these patients had other concurrent ocular disease that could affect vision. The mean (SD) hemoglobin level of our patients was 12.44 (1.78) g/dL (124.4 [17.8] g/L). There was no history of sleep apnea in any patient. We also recruited 9 patients (16 eyes) who were used as matched normal patients without retinal disease or systemic HTN or DM. Overall, 34 lesions and the surrounding retinas were evaluated with the microperimeter.

Microperimetry testing provides a subjective measure of a patient's visual function in a relatively small area of their retina (10°-20°). With the use of the Spectral OCT scanning laser ophthalmoscope (SLO) combination imaging system (OPKO Instrumentation, Miami, Florida), providing confocal fundus images for alignment, orientation, and registration, the map produced by this testing modality allows the operator to know precisely what fundus location is being stimulated.
During a microperimetry test, a patient is shown visual stimuli at specific light intensities at specific locations on his or her retina. The patient uses a handheld button/clicker to notify the system if the stimulus is seen. That feedback (or lack thereof) determines the next intensity of the subsequent stimulus. This process is repeated for all of the stimuli in a predetermined pattern and predetermined area. At the end of the test, the operator is given a fundus image with the stimulus pattern overlaid showing the dimmest intensity at which each stimulus was seen by the patient. The intensity level of the stimulus is displayed in decibels.

We designed a custom pattern of 13 test points, which we term the 9-4 pattern (Figure 1). This was designed to have symmetrical group of 9 test spots to be used in the area of resolved CWSs surrounded by 4 adjoining points that were 950 µm from the center of grid, which we used as controls for uninvolved retina. We chose a Goldmann III spot size with starting stimulus of 10 dB and 150 milliseconds’ duration. These parameters allowed for detection of the lesion without triggering eye movements. The use of the 9-4 pattern resulted in a short test time and helped eliminate patient fatigue. Our goal was to determine retinal sensitivity but to avoid patient fatigue. We therefore used a +2 strategy as recommended by Convento and Barbaro.12

The fixation target was a white cross. The mobility of the fixation target allows for testing beyond the arcades and at specific designated locations. We used the 8-frame-per-second eye-tracking software, which tracked and adjusted for eye movement. We used the 4-spot pattern in each eye for the patient to practice. This was done to correct for the learning effect known to occur with computerized perimetry.13 Prior to testing, the patients’ color photographs were reviewed to ensure that the correct area of the retina, corresponding to the CWSs, was being tested.

The test was administered 5 minutes after the practice session, and a 15-minute rest period was given between testing of the right and left eyes. The test was performed on the eye with better vision first in order for the patient to become familiar with the testing method. To confirm the test point hit the CWS lesion exactly, the microperimetry map was overlaid onto the color fundus photograph using photoediting software (version 10.0.1; Adobe Photoshop CS3, San Jose, California) (Figure 2).

The deepest scotoma in the central 9-point field in the area of the CWS was the value used for the scotoma. For the adjacent control retina, we averaged the adjacent points around the grid to determine non-CWS retina sensitivity. Any test spot overlapping a vessel was discarded because blood vessels reduce retinal sensitivity when testing with microperimetry. For statistical analysis, we used a paired t test and JUMP software (version 8.0; SAS Institute Inc, Cary, North Carolina).

RESULTS

We evaluated 28 retinal CWSs in 12 patients. There were 6 hypertensive lesions in 6 patients with HTN, and there were 28 diabetic CWSs in a total of 6 patients with DM (Table 1). For normal controls, there were 34 areas tested in 16 eyes of 9 patients. For each CWS in the study population we chose 1 age- and location-matched area in normal patients as controls.

Microperimetric sensitivity showed that the mean (SD) sensitivity of HTN CWSs was 11.67 (3.88) dB. The mean sensitivity of surrounding controls from HTN CWSs was 14.00 (2.89) dB (Figure 3). The mean sensitivity of age- and location-matched normal controls was 13.33 (3.27) dB. Sensitivity of HTN CWSs was statistically different from the surrounding control area (P = .01), but not from age- and location-matched normal control regions (P = .26). There was no significant difference between the surrounding control in the hypertensive eyes and that of the age- and location-matched normal eyes (P = .64).

Microperimetric sensitivity showed that the mean (SD) sensitivity of DM CWSs was 7.21 (5.48) dB. The mean sensitivity of surrounding control areas from DM CWSs was 11.80 (3.45) dB (Figure 3). The mean sensitivity of age- and location-matched normal control areas was 15.28 (2.45) dB (Figure 4). Among patients with DM,
the retinal sensitivity over resolved CWSs was decreased compared with adjacent control areas \( (P < .001) \). Not surprisingly, the retinal sensitivity overlying resolved CWSs in patients with DM was decreased compared with age- and location-matched normal control retinal areas \( (P < .001) \). However, the adjacent control areas among patients with DM were decreased compared with age- and location-matched normal controls.

This difference implies that the diabetic retina not visibly involved with CWSs has lower retinal sensitivity. In addition, there was a statistically significant difference between the mean sensitivity of hypertensive CWSs and the mean sensitivity of diabetic CWSs \( (P = .045) \) (Table 2). The difference in mean retinal sensitivity between our control groups was not found to be statistically significant \( (P > .10) \). The difference is likely due to the fact that we used age- and location-matched normal controls to correspond to our patients with HTN and DM and CWSs (Figure 5).

**Table 2. Sensitivity for Patients With Hypertension (HTN) and Diabetes Mellitus (DM) Across Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal (Mean, SD)</th>
<th>Cotton-Wool Spots (Mean, SD)</th>
<th>Surrounding Control (Mean, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>13.33 (3.27)</td>
<td>11.67 (3.88)*</td>
<td>14.00 (2.89)*</td>
</tr>
<tr>
<td>DM</td>
<td>15.28 (2.45)\†,\§</td>
<td>7.21 (5.48)\†,\‡,\§</td>
<td>11.80 (3.45)\†,\§</td>
</tr>
</tbody>
</table>

*Group differences were tested by paired \( t \) test; the values that are labeled with the same symbol are significantly different from one another \( (P < .05) \).

**COMMENT**

Systemic vascular disease such as DM or HTN can cause inner retinal disease by damaging the retinal circulation. One of the obvious clinical signs of such damage is the retinal CWS, which represents axoplasmic debris in the retinal nerve fiber layer following an inner retinal infarction. Without microperimetry technology, it is difficult to assess the amount of vision loss and functional retinal damage due to these lesions. It has been shown that resolved CWS lesions have permanent structural consequences that have been documented by spectral domain OCT. Subsequent visual sensitivity consequences would be expected.\(^8\)\(^-\)\(^10\) It is likely that these lesions produce a combination of focal relative scotoma (owing to loss of ganglion cells in the region of the ischemic in-
can be corrected owing to the slow speed of the move-pixel, we will not see any effect of microtremor. Slow drift our opinion, owing to the pixel size of about 20 µm/rate of 8 frames/s or about 125 milliseconds/image. In

amplitude tremor, slow drifts, and fast microsaccades (du-

different fixation eye movements: high-frequency small-

and residual positional inaccuracy when studying CWSs.

may explain why there are different depths of scotomas 
some small positional errors during microperimetry. This 

completely ideal, however, because the 8-Hz tracker can cause 

the longer examination time period that would be needed.

Our study took advantage of several features of com-

primarily, a simultaneous infrared SLO image of the retina allowed precise microperimetry localization over the le-

ions in question. Also, we could customize programs and 

select targets outside the macula in areas peripheral to 

the major vascular arcades. Finally, eye movement is sta-

bilized using an eye tracker that ensures that the micro-

perimetry target is consistently over the retinal area of 

interest. To confirm reproducibility of microperimetry 
data, we evaluated 72 eyes in 36 patients using 2 sepa-

rate microperimetry sessions. We found that 95% of the 

retinal sensitivity value between the 2 examinations was 

within 4 dB (repeatability coefficient=4) using Bland-

Altman plot (Amini et al14). The eye tracker is not com-

bined SLO/microperimetry (OPKO Instrumentation). Pri-

evaluating the functional correlates of structural retinal 

areas. The use of microperimetry is an important tool in 

CWSs as well as in the adjoining apparently uninvolved 

severe than in hypertensive eyes both in areas of old 

HTN. The vision loss in diabetic eyes seems to be more 

reasons why the lesions may be different. One possibil-

ity is that patients with DM have a more impaired reti-

circulation prior to the arteriolar infarction causing the 

CWS; however, it is also possible that there is inability 

of the retinal circulation in the patient with DM to revascularize or the presence of more severe pericytic in-

jury in those with DM. What is also possible is that pa-

ients with HTN have less severe retinovascular disease 
than those with DM or compensate better after micro-

infractions.

In conclusion, our study has shown that there are fo-

areas of focal vision loss in patients with DM and HTN. The vision loss in diabetic eyes seems to be more 

severe than in hypertensive eyes both in areas of old 

CWSs as well as in the adjoining apparently uninvolved 

areas. The use of microperimetry is an important tool in 

evaluating the functional correlates of structural retinal 

changes.

Accepted for Publication: September 20, 2010. 
Correspondence: William R. Freeman, MD, Jacobs Retina 
Center, 0946, University of California, San Diego, 9415 
Campus Point Dr, No. 0946, La Jolla, CA 92093-0946 
(freeman@eyecenter.ucsd.edu).

Financial Disclosure: None reported. 
Funding/Support: Support was provided by the Inje Re-

search and Scholarship Foundation 2009 (to Dr Kim), 
EY016323 (to Dr Bartsch), National Institutes of Health 
grant EY07366 (to Dr Freeman), the Foundation for Fight-

ing Blindness Inc, and an unrestricted grant from the Ja-

oks Retina Center.
REFERENCES


Archives Web Quiz Winner

Congratulations to the winner of our February quiz, Arun Lakshmanan, MS, DNB, FRCS, MRCOphth, Department of Ophthalmology, Queens Medical Centre, Nottingham, England. The correct answer to our February challenge was acute macular outer retinopathy. For a complete discussion of this case, see the Small Case Series section in the March Archives (Yeh S, Hwang TS, Weleber RG, Watzke RC, Francis PJ. Acute macular outer retinopathy [AMOR]: a reappraisal of acute macular neuroretinopathy using multimodality diagnostic testing. *Arch Ophthalmol*. 2011;129[3]:365-368).

Be sure to visit the Archives of Ophthalmology Web site (http://www.archophthalmol.com) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also be able to choose one of the following books published by AMA Press: *Clinical Eye Atlas*, *Clinical Retina*, or *Users’ Guides to the Medical Literature.*