Objective perimetry based on chromatic multifocal pupillometer for treatment follow-up and diagnosis in patients with retinal and macular dystrophies

Ygal Rotenstreich, MD

1. Director, Hereditary Retinal Dystrophies and Electrophysiology Unit
2. Director, Retinal Research Laboratory

Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel
The Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
Financial disclosure

Accutome Inc.
Visual Feld constriction in optic nerve and retinal degeneration

Glaucoma - >60M

Retinitis pigmentosa (RP) - >1.5M

Photos: National Eye Institute, National Institutes of Health

Fig. 1

Fig. 2

Fig. 3
Subjective perimetry and its limitations

- Patients’ cooperation is essential
- Prolonged and tiresome
- Qualified personnel
- The test can’t distinguish between optic nerve vs. retina pathologies
Perimetry based on Pupillary Light Reflex to multifocal chromatic stimuli

- Objective
- More informative
- Applicable to all pathologies and patients

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cones</td>
<td>Low-intensity red (624 nm)</td>
</tr>
<tr>
<td>Rods</td>
<td>Low-intensity blue (485 nm)</td>
</tr>
<tr>
<td>ipRGCs</td>
<td>High intensity blue (485 nm)</td>
</tr>
</tbody>
</table>
The Multifocal Chromatic Pupillometer - 76 Points (2mm) - 18° Visual Field

©Accutome, PA
The multifocal chromatic pupillometer
Study design:

• 13 retinitis pigmentosa (RP) patients

• 17 healthy age-matched volunteers

• In RP patients, the chromatic pupillometer recordings were compared with their dark-adapted Chromatic Goldmann
The test protocol

• Non-tested eye is covered by a patch
• Stimulus duration - 1 second
• Tracking of pupil size - 4 seconds
• Chromatic stimulus
  – Red (1000 cd/m², 624nm)
  – Blue (200 cd/m², 485nm)
Test Parameters:

Maximal Pupil Contraction

Velocity

% Pupil Contraction

Time of Maximal Contraction Velocity
In healthy subjects: PLR to blue and central light stimuli are stronger than to red and peripheral stimuli.
RP patients: reduced response to blue light, correlating with VF restriction severity

% Pupil contraction

Maximal Contraction Velocity

Time of Contraction Velocity
RP patients: milder reduction in PLR to red light

% Pupil contraction

Maximal Contraction Velocity

Time of Contraction Velocity
### Case I – patient with no light detection

**DA-GVF**

<table>
<thead>
<tr>
<th>Blue</th>
<th>No light detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPC</td>
<td><img src="image" alt="PPC Diagram" /></td>
</tr>
<tr>
<td>MCV</td>
<td><img src="image" alt="MCV Diagram" /></td>
</tr>
<tr>
<td>LMCV</td>
<td><img src="image" alt="LMCV Diagram" /></td>
</tr>
</tbody>
</table>

**Red**

<table>
<thead>
<tr>
<th>No light detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPC</td>
</tr>
<tr>
<td>MCV</td>
</tr>
<tr>
<td>LMCV</td>
</tr>
</tbody>
</table>
Case II – patient with VF restriction

Red

Blue

DA-GVF

PPC

MCV

LMCV

<1SE

1SE-2SE

2SE-3SE

3SE-4SE

4SE-5SE

>5SE

Red

Blue
Variability in the time to maximal velocity of contraction was significantly higher in RP patients compared with controls ($p<0.0001$, AUC=0.97)
Linear negative correlation between the subjective VF (chromatic Goldmann) and the variability in the time parameter

\[ y = -0.2835x + 0.3829 \]

\[ R = 0.67 \]
Best disease - Vitelliform macular dystrophy

• Autosomal dominant disease that affects the retinal pigment epithelium (RPE) at a very young age.
• Characterized by lipofuscin accumulation in the RPE.
• In these patients an eccentric preferred retinal locus is taking over, leading to a discrepancy between retinal damage and Humphrey’s perimetry.
Study design

• 5 Best patients

• 17 healthy individuals

• The pupillary responses of Best patients were compared with the pupillary responses obtained from normal control subjects and with their findings on Humphrey's 24-2 perimetry and OCT.
Best’s patients: reduced PLR to red light

<table>
<thead>
<tr>
<th>Blue</th>
<th>Red</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPC</strong></td>
<td><strong>MCV</strong></td>
</tr>
<tr>
<td>16 15 17 23</td>
<td>34 35 35 38</td>
</tr>
<tr>
<td>13 19 14 19 20 22</td>
<td>29 50 28</td>
</tr>
<tr>
<td>20 17 21 14 20 22 23 18</td>
<td>34 36 41</td>
</tr>
<tr>
<td>19 15 16 21 21 13 20 14 17 19</td>
<td>31 37 37 37 38 39</td>
</tr>
<tr>
<td>19 19 19 19 17 18 24 22 22 19</td>
<td>38 35 39 41</td>
</tr>
<tr>
<td>18 20 18 21 17 19 20 21 18 18</td>
<td>33 32 37 34</td>
</tr>
<tr>
<td>18 19 18 18 17 19 21 20 17</td>
<td>36 34 30 36 33</td>
</tr>
<tr>
<td>20 19 15 18 22 21 17</td>
<td>36 35 35 32</td>
</tr>
<tr>
<td>18 13 19 20</td>
<td>36 41 38 32</td>
</tr>
<tr>
<td>6 9 7 8</td>
<td>37 33 32</td>
</tr>
<tr>
<td>6 7 10 8 11 11</td>
<td>38 42 37</td>
</tr>
<tr>
<td>7 7 9 9 8 6 9 6</td>
<td>35 28 33 34</td>
</tr>
<tr>
<td>9 10 9 14 10 8 9 9 8 7</td>
<td></td>
</tr>
<tr>
<td>9 7 7 10 15 7 13 9 9 8</td>
<td></td>
</tr>
<tr>
<td>9 9 10 11 11 13 10 10 8 9</td>
<td></td>
</tr>
<tr>
<td>5 8 6 6 10 8 10 9 9 12</td>
<td></td>
</tr>
<tr>
<td>6 8 8 10 9 11 8 8</td>
<td></td>
</tr>
<tr>
<td>5 7 9 9 9 9</td>
<td></td>
</tr>
<tr>
<td>11 7 10 8</td>
<td></td>
</tr>
</tbody>
</table>
Best patient #1 – correlation with OCT and Humphrey 24-2 perimetry
Conclusions

• The chromatic multifocal pupillometer enables non-invasive objective diagnosis of macular and peripheral defects

• Significant rod deficit was demonstrated in RP patients, correlating with their subjective VF detected

• Significant cone deficit was demonstrated in Best patients, correlating with their OCT findings while subjective VF detected a smaller defect.
### Objective

**Differential diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>Best</th>
<th>Retinitis Pigmentosa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulus more affected</strong></td>
<td>Red</td>
<td>Blue</td>
</tr>
<tr>
<td><strong>Parameter more affected</strong></td>
<td>Time - Shorter</td>
<td>Time Longer /Velocity</td>
</tr>
<tr>
<td><strong>Variability in time</strong></td>
<td>Same as normal</td>
<td>High</td>
</tr>
<tr>
<td><strong>% constriction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>Reduced very mild</td>
<td>Reduced moderate</td>
</tr>
<tr>
<td>Red</td>
<td>Reduced mild</td>
<td>Reduced mild moderate</td>
</tr>
<tr>
<td><strong>Maximal velocity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>Reduced mild</td>
<td>Reduced Severe</td>
</tr>
<tr>
<td>Red</td>
<td>Reduced mild moderate</td>
<td>Reduced moderate</td>
</tr>
<tr>
<td><strong>Time to max velocity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>Shorter moderate</td>
<td>Longer Severe</td>
</tr>
<tr>
<td>Red</td>
<td>Shorter moderate</td>
<td>Longer moderate severe</td>
</tr>
</tbody>
</table>
Response consistency in serial testing of normal subjects Red & Blue

Percentage contraction

Max Velocity

Time of Max Velocity

\[
\begin{align*}
\text{Re-test value} & : R = 0.751, P < 0.001 \\
1^{\text{st}} \text{test value} & : R = 0.521, P < 0.001 \\
1^{\text{st}} \text{test value} & : R = 0.258, P < 0.001
\end{align*}
\]

N = 830
New large clinical trial
Objective perimetry based on chromatic multifocal pupillometer
30 degree visual field

Glaucoma, Retinitis Pigmentosa, AMD, Diabetic Retinopathy
Clinical trial design – 30 degree VF

- Study population
  - 90 healthy control subjects, 40 Retinitis Pigmentosa patients, 40 Glaucoma patient, 40 diabetic retinopathy, 40 Adult macular degeneration patients

- Chromatic stimulus
  - Red (1000 cd/m², 624nm)
  - Blue (170 cd/m², 485nm)

- Stimuli will be presented by 76 LEDs in a 30-degree visual field.

- The pupillary responses of the patients will be compared with control group

- All subject will also be tested in: 1) Humphrey perimetry, 2) OCT, 3) Optometrist exam, 4) Color vision test.
Preliminary results - Glaucoma patient #1

Humphreys

PPC-red
The pupilometer maybe used for early diagnosis of:

- Traumatic Brain Injury (TBI)
- Alzheimer disease
- Parkinson disease

Studies are currently underway
Acknowledgements

Current Team
- Dr. Ifat Sher
- Dr. Mohamad Mhajna
- Dr. Soad Haj Yahia
- Ron Chibel
- Daniel Ben Ner
- Adi Tzameret
- Sapir Kalish
- Nir Levy
- Victoria Edelstein
- Biniaminov Luba
- Inesa Kelner
- Ravit Getenuo

Past team members
- Dr. Skaat Alon
- Dr. Kolker Andrew
- Dr. Adham Matani
- Dr. Kinori Michael
- Dr. Attar-Ferman Gili

Collaborations:
- Prof Laurence Freedman, The Gertner Institute, Israel
- Prof. Belkin Michael: Tel Aviv University, Israel
- Prof. Haratz Dror: Lipid Center, Tel Hashomer, Israel
- Prof. Arnon Nagler: Tel Hashomer, Israel
- Dr. Avi Treves: Tel Hashomer, Israel
- Dr. Aviv Shaish: Lipid Center, Tel Hashomer, Israel
- Prof. Ninette Amariglio: Tel Hashomer, Israel
- Prof. Nathali Savion: Tel Aviv University, Israel
- Prof. Abraham Zangen: BGU, Israel
- Prof. Michal Schwartz: Weizmann Institute
- Prof. Michael Eisenbach: Weizmann Institute
- Prof. Shlomo Margel: Bar Ilan University