Learning Objectives:
At the end of this presentation, the participants will:

1. Understand the principles behind Vision Restoration Therapy (VRT)
2. Be able to determine what patients may benefit from VRT
3. Know where VRT is being performed within the United States
4. Know the inclusion and exclusion criteria for VRT
5. Know the potential explanations for apparent visual field improvement after VRT

CME Questions:
1. What is VRT?
   a. A computer-based training program
   b. A type of visual field test
   c. A test of contrast sensitivity
   d. A way to monitor eye movements

2. Where is VRT performed?
   a. In a hospital
   b. In an outpatient clinic
   c. At home
   d. In a laboratory

3. What is an ARV?
   a. A type of off-road mode of transportation
   b. An area of residual vision within or adjacent to a visual field defect
   c. A scotoma in an otherwise full visual field
   d. A type of eye movement

4. All of the following are inclusion criteria for VRT except
   a. The defective area of the visual field should affect the central 30-degree visual field
   b. A central residual visual field of at least 5 degrees horizontally and vertically should be spared
   c. The patient has had a stroke, subarachnoid hemorrhage, or cerebral injury
   d. The visual field defect must be related to an optic neuropathy, homonymous visual field defect, or retinopathy

5. The percentage of patients who improve after VRT is:
   a. 10%
   b. 33%
   c. 67%
   d. 100%

6. The percentage of patients who will note an improvement in one or more daily activities after VRT is:
   a. 20%
   b. 40%
   c. 60%
   d. 80%

Key Words: Visual field restoration therapy

FUNDAMENTALS

What is VRT?
NovaVision VRT™ Vision Restoration Therapy™ (VRT) is a computer-based training program developed to improve visual function in patients with visual field defects due to brain damage (1-3). By presenting thousands of visual stimuli at the border of the visual field defect and simultaneously giving little stimulation to the intact sector of the visual field, VRT attempts to improve function in areas of “residual vision” (4) that may not be appreciated or perhaps may be neglected by the patient; i.e., areas of “relative defect.”

How was VRT developed?
The basic idea that training visual function may be beneficial dates back to observations in the late 1970s by researchers in Germany who observed visual field border shifts after repeated perimetric testing (5). Subsequently, studies were initiated using extensive training with standard perimeters in laboratory sessions (6). The studies were extremely laborious and although they seemed to indicate that the visual field could be expanded slightly, the methods were criticized (7) and the studies were subsequently discontinued. In the early 1990s, two scientists at the University of Magdeburg (E. Kasten and B.A. Sabel) re-addressed the issue using personal computers to permit a standardized, automated vision training program (1-4, 8-)
10). This allowed patients to carry out the training at home with feedback provided by the researchers. Several clinical studies in Germany by the Sabel group (2, 3) convinced these researchers that this type of training program could improve the visual field—at least to some extent—in patients with a variety of visual field defects, both homonymous defects and those defects related to optic nerve injury. In order to provide the public with the means to undergo such training on a wider basis, a company called NovaVision was formed. The product, called “Vision Restoration Therapy” was introduced into the German market in late 1999. In 2003, the FDA cleared the commercialization of VRT in the United States. The first patients were treated in the United States in 2004.

What does VRT entail?
VRT is a home-based rehabilitation regimen. It does not require therapy sessions in hospitals or outpatient ambulatory settings. Before starting VRT, a patient must undergo a diagnostic evaluation at a clinical center that offers the therapy. The principal aim of this diagnostic session is to determine if the patient is fit to carry out an extensive therapy regimen on a computer and to check for possible exclusion criteria (such as epileptic photosensitivity, significant cognitive deficits, etc.). If the patient qualifies, “areas of residual vision” (ARVs) are localized using NovaVision high-resolution perimetry (HRP). ARV charts are then used by NovaVision Inc. to create customized therapy parameters for each patient based on his or her performance. The therapy software together with the therapy device is then sent to the patient, who trains for 1 hour a day (two 30-minute sessions), 6 days a week. Approximately every 4 weeks, the patient sends his or her results to NovaVision so that adjustments can be made to the therapy parameters based on evidence of any recovery of visual function. After 6-7 months of VRT, the patient is encouraged to return to the local clinical center for a final assessment.

What are the proposed mechanisms?
The Sabel group believes that areas of residual vision and even blind regions of the field, particularly those near the border of seeing and non-seeing field, are subserved by neurons that have managed to survive the injury but are insufficient to drive function above threshold (1, 2, 10). They postulate that by regularly exposing these neurons to functional tasks, the gain of the neurons may be increased, providing perception in previously non-perceived areas of the field. Sabel and his group also believe that VRT induces or stimulates latent plasticity in the CNS, such as that found in visual receptive field studies following retinal (11) or cortical (12) injury. There is no solid evidence to date that such mechanisms actually operate in humans undergoing VRT, and this theory clearly requires experimental verification.

More recently, Sabel et al. have proposed that there may be several other mechanisms contributing to the apparent improvement in visual field during and after VRT, including improvements in reaction time (9, 10) and neuronal activation by localized attention (13). Such mechanisms are not on the sensory side but rather involve cognitive processing. Based on this theory, the scenario would be that areas of partial injury exist after damage (14, 15). These could be “penumbra,” as in the surround of ischemic lesions of the brain, or they could result from partial deafferentation. These residual visual capacities can be improved by activating them via attention, a “top-down” influence that reaches ARVs from higher visual centers. The evidence for a role of attention in restoration is compelling: in some patients, “square-like” visual field border shifts were observed in patients in whom a focal, square-shaped attention cue was used (13). Nevertheless, the question as to which mechanisms are induced by VRT requires further study, particularly as some researchers believe that the “improvement” in visual fields seen in patients during and after VRT is related not to true improvement in the field as claimed by Sabel et al. but rather to minute shifts in fixation (see below).

What studies have been performed that support its use and what are the results?
Most published VRT studies to date have come from the Sabel group. They initially published a pilot trial with a few patients (3) and followed this with a double-blind, randomized, placebo-controlled trial (2) and other studies (1, 9, 10, 13). In addition, as noted above, Zihl and colleagues (5, 6) as well as others have reported evidence of restoration of visual fields by intensive training, although all of these groups have used their own methods of investigation (16-19) and the tasks the patients had to perform were not identical with VRT (including not being as standardized).
VRT has been reported to result in improved detection in a super-threshold campimetric task (HRP, 2, 3, 9, 10, 13), a reduced number of misses (defects) during standard perimetry (9, 10, 13), improved reaction time in stimulus detection tasks (9, 10), improvements in a neuro-visual paper and pencil task (the ZVT-test) (2), and, in about 80% of patients, subjective improvements in various activities of daily living, including visual confidence, reading, mobility and navigation (9).

The joint Tübingen-Magdeburg study challenged the belief that VRT works by activating visual neurons and proposed that the results of VRT represented changes in fixation that can only be detected by performing perimetric tests using SLO (20) as both the stimulus and to monitor fixation. However, even in this study, although the visual field borders were found to be unchanged when measured with SLO perimetry (20), both super-threshold perimetry and near-threshold perimetry did show improvement (10). Clearly, an independent study would be an important step forward, particularly one in which a placebo or sham arm was included or another form of stimulation was used. Some researchers in the US are currently studying VRT vs. sham VRT for selected patients with visual field defects from a variety of conditions, including optic neuropathies.

PRACTICAL MATTERS

Where in North America is VRT offered?

**California**
Sharp Memorial Hospital, San Diego
Sharp Chula Vista Medical Center, Chula Vista
Sharp Grossmont Hospital, La Mesa

**Florida**
Bascom Palmer Eye Institute - University of Miami Vision Restoration Clinic, Miami
HealthSouth Sunrise Rehabilitation Hospital, Sunrise Intercoastal Medical Group, Sarasota
Morton Plant Hospital, Clearwater
Tallahassee Memorial HealthCare Rehabilitation Center, Tallahassee

**Georgia**
Emory Healthcare Eye Center, Atlanta

**Maryland**
Johns Hopkins University, Wilmer Eye Institute, Baltimore
Total Rehab Care at Washington County Hospital, Hagerstown

**Michigan**
Kresge Eye Institute at Wayne State University School of Medicine, Detroit

**Nebraska**
Richard H. Legge, M.D., Omaha

**New Jersey**
New Jersey Neuroscience Institute at JFK Medical Center, Edison

**New York**
Beatrice Engstrand, MD, Huntington Neurological Institute of New York at Columbia University Medical Center, New York Rusk Institute of Rehabilitation Medicine at New York University, New York

**Oregon**
Oregon Health & Science University, Casey Eye Institute, Portland

**Pennsylvania**
Albert Einstein Medical Center, Philadelphia

To whom should VRT be offered?
VRT is currently being offered to patients with brain injury, usually from stroke or brain trauma who typically have incomplete homonymous hemianopias. In addition, some clinics are offering VRT to patients with incomplete bitemporal field defects from chiasmal dysfunction and to patients with optic nerve-related visual field defects.

When should VRT be offered?
VRT can be started as soon as the patient is able to sustain sufficient attention to carry out a computer-based task for at least 15 minutes or longer. Published studies have all been performed on subjects in whom the lesion age was at least 6 months to reduce the likelihood that any improvement in the visual field was the result of spontaneous recovery. To date, there are no data regarding whether beginning VRT immediately after an injury would be more beneficial than its use in
patients with more chronic visual field loss. Obviously, such a study would need to be case-controlled.

**What factors influence the outcome of VRT?**
Despite numerous correlation analyses of outcome with different patient variables, only one variable consistently correlates with outcome: the size of the ARV (9, 10). Thus, the more “relative” the field defect, the more likely patients with an apparently chronic, stable visual field defect will show improvement. Factors that don’t seem to correlate with outcome include the age of the patient, the age of the lesion (although, as noted above, no studies have assessed the results of VRT in patients with acute visual field loss), and the cause of the field defect (9).

**What screening should be performed before VRT is offered?**
NovaVision has established a set of defined inclusion and exclusion criteria to determine if a patient is a candidate for VRT. These are as follows:

**GENERAL INCLUSION CRITERIA**

The typical patient will have sustained a visual field defect from a lesion of the brain or of one or both optic nerves. The visual field loss should be documented by automated static perimetry, ideally using the Humphrey field analyzer; however, other measures of computerized visual field testing or even non-computerized perimetry are acceptable.

- The defective area should affect the central 30-degree visual field (more peripheral defects can not be treated with the NovaVision medical device).
- A central residual visual field of at least 5 degrees horizontally and vertically should be spared.

Typical neurological lesions would be:

- Traumatic Brain Injury (TBI), Closed Head Injury, Penetrating Head Injury
- Stroke—ACA, ICA, PCA, MCA, and Vertebro-basilar strokes
- Subarachnoid Hemorrhage
- Cerebral Aneurysm
- Arteriovenous Malformation (AVM)
- Brain Hemorrhage of other cause
- Brain Tumor (meningioma, craniopharyngioma, low-grade glioma, etc.)
- Encephalitis (fully recovered)

**Note:** There is no published evidence that visual field loss from epiretinal membrane, macular degeneration, retinal vascular occlusion, retinitis pigmentosa, or injury to the eye itself can be treated with VRT. Also, no research has been published with specific respect to the effects of VRT on visual field loss from nonarteritic or arteritic ischemic optic neuropathy or, for that matter, ANY optic neuropathy (e.g., traumatic, Leber).

The patient should be at least 12 years of age (patients younger than 18 years of age need to have full support of parents/caregivers in regards to performing the therapy on a regular basis).

**GENERAL EXCLUSION CRITERIA:**

**Medical History/Patient Charts:**

- The patient has best-corrected visual acuity (BCVA) worse (less) than 20/200 on EDTRS or Snellen chart in the better-seeing eye.
- The patient suffers from large amplitude or convergence-induced nystagmus in primary position (patients with gaze-evoked nystagmus are not excluded)
- The patient has evidence of visually significant chorioretinal, retinal vascular, or corneal disease.
- The patient has an active seizure disorder. This includes patients with photosensitive epilepsy or who have suffered a seizure within the past 3 months with no change in treatment.
- The patient has any kind of dementia (e.g., scores less than 20 on the Mini-Mental Status Exam (MMSE).
- The patient has a terminal illness and is expected to survive less than 1 year.
- The patient has active multiple sclerosis, associated acute optic neuritis that occurred within the past 6 months, motor function changes within the past 3 months or a combination of these.
- The patient has active inflammatory neurological or eye disease. VRT can be started after the inflammation has subsided. (Check with attending neurolo-
gist or eye-care provider).
- Patients who suffer from chronic migraine aura with or without headache are not eligible for VRT until the aura have not occurred for at least 3 months and progressive brain disease has been ruled out.
- NovaVision VRT is not indicated for treatment of patients suffering from hemilateral neglect without visual field loss.
- Note: Prosopagnosia is NOT an absolute contraindication for VRT.

Medical History/Patient Charts or Observation/Performance During NovaVision Diagnostic Testing:
- The patient is unable to sit upright, unsupported for at least 15 minutes.
- The patient cannot maintain alertness without prompting for 15 minutes. Evidence of such a problem may include closing eyes, falling asleep despite adjusting of parameters to more allowable limits, etc.
- The patient has motor impairment that prevents consistent operation of the VRT input device with either hand (or foot).
- The patient has no clear motivation for undergoing VRT. (The patient should be able to identify a goal to achieve for undergoing VRT).

Confounding Performances During NovaVision Diagnostic Testing:
- The patient does not understand the requirements of the program, (e.g., the patient does not respond to light stimuli or fixation control despite repeated instruction).
- The patient is unable to clearly and consistently see a fixation stimulus of no greater than 15 pixels and appreciate color or shape change consistently.
- The patient is unable to maintain satisfactory fixation despite verbal redirections for 10 minutes of Status testing. Satisfactory fixation is considered:
  a) a 90% fixation accuracy rating with a stimulus of no greater than 15 pixels on a testing grid of 19x15 OR
  b) independent of fixation rate, observation of patient during testing confirms no or very little visual scanning.

The NovaVision VRT Candidate Inclusion/Exclusion Criteria are a guideline for candidate selection. There may be exceptions and patients not meeting all criteria may be regarded as being candidates for VRT. The ultimate decision about selecting a patient for VRT is up to the Partner Clinic.

Some clinics choose to screen candidates with standard automated perimetry (eg, Humphrey SITA-standard programs) to assess patient capability to perform computerized visual tasks. Assessing if a patient’s expectations are realistic is also crucial in deciding whether or not to recommend therapy. Patients who meet the inclusion criteria are then screened with a high-resolution perimetry (HRP) medical device provided by NovaVision. This procedure determines the size and location of ARVs that then form the basis for parameter settings of the training regions and subsequent feedback to the patient.

What should a patient be told about the potential benefits of VRT?
Patients are told that about 1/3 of patients will not experience any improvement, 1/3 will experience some degree of improvement, and 1/3 will experience substantial improvement (9, 10). Based on patient testimonials alone (not corroborated with specific testing), patients are told that there is an 80% chance that they will be able to perform some daily visual tasks with more confidence. Especially in those patients where the scotoma is close to fixation, a few degrees of gain can have large subjective benefits. However, it is emphasized to all patients with significant homonymous hemianopias that it is extremely unlikely that they will recover sufficient visual field to be able to legally drive in their particular State. Clearly, this distresses many patients for whom the loss of the ability to drive is their main reason for seeking alternative therapies.

How much does VRT cost?
Most clinical centers charge each patient approximately $6000, about half of which goes back to the company and half to the individual clinic. Unfortunately, this treatment currently is not covered by most insurance carriers (exceptions have been some workman’s compensation plans and the military but some progress is being made in this regard.
What is the long-term outcome of VRT?
Studies performed by the Sabel group indicate that the improvements in performance after VRT are maintained for at least a year following completion of the 6-month course of treatment.

CRITICAL ISSUES

Other than the proposed mechanism, what are other possible explanations of “positive” results?
It may very well be that factors other than true enlargement of the visual field (i.e., reduction in the size of the visual field defect) contribute to the VRT-induced subjective improvement. Mueller et al. (9) observed what they termed a “mismatch” between objective visual field enlargement and subjective improvement after VRT in a small proportion of the patients. Thus, other factors, such as perception and attention, may well contribute to the clinical results. Indeed, Mueller et al. noted an improved reaction time in the intact visual field of patients after VRT, suggesting that repetitive stimulation heightens awareness of both non-seeing or at least non-used areas of the field as well as intact or normally perceived areas.

Some critics of VRT claim that the apparent improvements in the visual fields are due to minute changes in fixation; i.e., the patient has learned to fixate eccentrically during the training (21-23). Sabel and his colleagues believe this explanation to be highly unlikely given the constant requirement of the patients to respond to a fixation task (i.e., color changes of the fixation spot). Sabel et al. have also pointed to the study performed by Reinhard et al. (20), which failed to identify any shifts of fixation in patients undergoing VRT, as being evidence for lack of eccentric fixation in the improvement of such patients; however, it is possible that by monitoring the patients with SLO, “normal” stimulation of eye movements by VRT was suppressed. Finally, if fixation shifts were responsible for the apparent improvement in the visual fields of patients after VRT, one would assume that border shifts would be consistent across the entire border of seeing and non-seeing field. In fact, this is not the case (10, 13, 24). Border shifts often occur in some regions of the visual field but not in others, including across the horizontal border of some patients with quadrantanopias (24). The selective border shift when patients are given an attentional cue is an example of this (13).

In addition, in standard perimetry, the blind spot is unchanged and fixation performance does not decline but in many cases actually increases after VRT (2, 9, 10, 13). This would not be expected if patients had unstable fixation or eye movements.

Another criticism proposed by Horton (22) concerns the role of saccadic eye movements. According to his theory, patients undergoing VRT “cheat” by moving their eyes during final outcome evaluation (but presumably not during the initial diagnostic testing). The argument essentially revolves around the idea that before VRT patients have stable fixation, whereas VRT stimulates them to preferentially shift fixation toward the blind field, thus producing an apparent but not true border shift. Perhaps inconsistent with this theory is that fixation reliability actually improves over the course of VRT, and the same arguments against the “eccentric fixation shift” (see above) would also be valid here. However, although there is no definite evidence supporting this artifact claim, there is no definite evidence against it. It is thus clear that in subsequent studies, eye movements should be monitored using some type of objective device.

What is SLO, how is it performed, what are its advantages, and what are its potential drawbacks?
The scanning laser ophthalmoscope is an instrument that presents visual stimuli to the retina while the fundus is observed and videotaped. In fact, at least two stimuli are present during testing: one is a constant stimulus used to stabilize and monitor fixation more precisely than can be achieved by simple observation through the viewing device that is typically used during standard static and kinetic perimetry. One or more stimuli are then presented to various parts of the field. The well-recognized advantage of SLO perimetry is its ability to control for possible small shifts in fixation. By studying the videos made during the procedure, the experimenter can determine if at any time, patients are not fixating steadily. He or she can then discard responses made at that time. SLO is said to have an accuracy of about 1 degree. As with other forms of perimetry, the SLO can present different kinds of stimuli. In the study by Reinhard et al. (20), for example, the authors did not use the stimulus paradigms used in standard perimetry but instead altered the psychophysical characteristics in several respects (i.e., they used a bright red background and a black target stimulus). In addition, the patients were not presented with a single stimulus but instead were required to perform a con-
scious discrimination task. They were presented three stimuli and had to verbally indicate how many stimuli they saw. Sabel, who was a co-author on this paper, has argued that this makes it difficult to compare the perimetric results using the SLO with the results of the other perimetric studies (10). Indeed, when Sabel et al. compared the visual fields obtained using conventional perimetry and super-threshold perimetry with the SLO results of the same patients, the SLO deficit was found to be significantly larger than with either of the other perimetric tasks. This suggests that the SLO perimetry as performed was too difficult for the damaged visual field to perform, resulting in relative defects appearing absolute on SLO perimetry (10).

OUTLOOK
What other studies of VRT are currently being performed?
At Emory, VRT and sham VRT are being compared in AION patients with altitudinal visual field defects that split fixation. In addition, there are at least two other groups in the US that are currently using brain imaging methods to study brain activation before and after VRT as physiological indicators of brain plasticity (University of Miami, Columbia University). In addition, the Sabel group is assessing VRT in children with brain damage.

What studies should be performed to clarify the controversy regarding VRT?
As in any areas of research, fundamental new findings tend to raise more questions that they answer. Thus, progress in this field can be made by answering the next obvious questions: (i) what changes, if any, occur in eye movements and eye movement strategies during and after VRT?; (ii) can the apparent improvement in visual field defects in some patients following VRT be confirmed by independent investigators?; (iii) what activities of daily living should be used for outcome assessment in evaluating the effects of VRT? and (iv) does earlier intervention in certain (or all) settings result in an improved outcome compared with the natural history of the underlying injury and its visual consequences?

OTHER THERAPIES
Besides VRT, what other options do we have to patients with visual field impairments?
An alternative approach that has been proposed to treat visual field defects is usually referred to as the “compensation” technique. The idea here is to ask the patient to move his or her eyes around more to improve scanning of the visual world. Such studies have been conducted in Germany (25–29) and in the UK (30, 31). It is too early to tell if such exercises are of practical benefit to the patients beyond the laboratory setting, particularly since, to our knowledge, no placebo-controlled trials have been performed. It would be most interesting to compare the practical benefits of this form of therapy with VRT with respect to subjective reports of visual improvement in certain activities of daily living.

References


CME Answers:
1. a
2. c
3. b
4 d
5. c
6. d