

# Original Research: Pupillary Constriction Velocity and Latency to Predict Excessive Daytime Sleepiness

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## Abstract

**Background:** Excessive daytime sleepiness (EDS) is common in adults. A need exists for an easier and faster objective clinical measures of EDS. The autonomic nervous system controls pupil size and prior pupillometry studies have demonstrated associations with sleepiness. We used a novel portable device to assess pupillometry and prospectively evaluated a sleep clinic cohort. **Methods:** Following IRB approval Pupillometry (The ForSite™, NeurOptics, Irvine, CA), was performed on 113 sleep clinic patients. Constriction and dilation velocity and latencies, minimum and maximum aperture were obtained along with Epworth Sleepiness Score (ESS), 10 point Visual Analog Scale (VAS), BMI, gender, age and AHI. Three sets of measures were obtained and analyzed with ANOVA, t-test, Linear Regression and Pearson correlation coefficients (SAS, Cary, NC). **Results:** Both constriction velocity and latency correlated with VAS ( $n = 88$ ,  $r = 0.28$ ,  $p = 0.007$  and  $r = 0.31$ ,  $p = 0.004$ ). Only constriction velocity correlated with AHI ( $n = 78$ ,  $r = -0.27$ ,  $p = 0.016$ ). Multivariate linear regression which includes VAS and age predicted constriction velocity ( $r = 0.36$ ,  $p = 0.002$ ) and latency ( $r = 0.38$ ,  $p = 0.001$ ). Using Pearson correlation, AHI and VAS combined were associated with constriction velocity ( $-0.273$  (0.016), and  $0.284$  (0.007), respectively). Using a maximum constriction velocity threshold value (age adjusted) of 2.8,  $VAS \geq 6$  was predicted with a sensitivity of 83% and specificity of 84%. **Conclusions:** Pupillary constriction velocity and latency predict self-reported VAS state of sleepiness. While both are affected by age, only constriction velocity is affected by apnea severity. These data suggest that a portable pupillometer may provide a method to identify individuals with abnormal sleepiness.

## Keywords

### Excessive Daytime Sleepiness, Pupillometry, Constriction Velocity, Constriction Latency

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## 1. Introduction

Excessive daytime sleepiness (EDS) is common in adults, it is very common clinical complaint in sleep clinic, it can be due to variety of reasons but most commonly due to sleep deprivation syndrome and Sleep Related Breathing Disorder, approximately 5% of adults complain of EDS [1] [2]. Sleepiness may present as increased propensity for sleep, decreased propensity for wake, or alterations in mood or neuro-cognitive function, pt. may present this complaint as tiredness, and evaluation of this complaint requires an awareness of various meanings of tiredness. The consequences of EDS can range from discomfort in social situation to life threatening such as falling asleep while driving. A public health threat with economic costs in the billions, drowsy driving is related to at least 100,000 motor vehicle accidents and more than 1500 deaths per year in United States [[www.sleepeducation.com](http://www.sleepeducation.com)].

EDS is a condition that can significantly reduce quality of life, decreases productivity and interferes with relationships if EDS persists neither normal nor healthy. One of the primary causes of EDS among Americans is self-imposed sleep deprivation. By some estimates, people now sleep about 20 percent less than they did a century ago. EDS is also linked with a number of primary sleep disorders, also caused by variety of physical and mental illnesses as well as some medications.

According to the results of NSF's 2008 "*Sleep in America*" Poll (National Sleep Foundation):

36 percent of Americans drive drowsy or fall asleep while driving (one of the most serious risk associated with EDS).

29 percent of Americans fall asleep or become sleepy at work.

20 percent of Americans have lost interest in sex because they are too sleepy.

14 percent of Americans report having to miss family events, work functions and leisure activities in the past month due to sleepiness.

Each of these consequences can have enormous impact on an individual's health, happiness and quality of life.

There are several self-rating scales available to rate severity of sleepiness e.g. Visual Analogue Scale (VAS) [3], Stanford Sleepiness Scale (SSS) [4], Epworth Sleepiness Scale (ESS) [5]. These depend on patient perception of sleepiness, motivation, and are subjective. The accepted objective clinical methods to assess sleepiness include the Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT); however, these are time and resource consuming. These tests are not portable and often cumbersome for patients and researchers. MSLT and MWT are not perfect tests, but they are the best objective tests currently available for characterization of ability to fall asleep and ability to remain awake respectively. A need exists (Institute of Medicine of the National Academics, 2006, Sleep Disorders and Sleep Deprivation) for an easier and faster objective clinical measures of EDS.

The autonomic nervous system controls pupil size and prior pupillometry studies have demonstrated associations with pupillary function affected by EDS. We used a novel portable device to assess pupillometry and prospectively evaluated a sleep clinic cohort. Currently, pupillometry is not a widely used clinical measurement of sleepiness, predominantly because the equipment is not readily available. Further research is necessary to determine the role of pupillometry in the assessment of daytime sleepiness in clinical practice.

### 1.1. Rationale

- 1) Sleepiness affects the Autonomic Nervous System
  - Sleep increases Parasympathetic tone (non REM).
  - Sleep decreases Sympathetic tone.
- 2) Pupillary Constriction velocity is a function of the balance between Sympathetic and Parasympathetic tone
  - Increased Sympathetic balance decreases constriction velocity.
  - Increased Parasympathetic balance increases constriction velocity.

### 1.2. Objective of Study

To evaluate portable pupillometry in measuring pupillary constriction velocity and latency (a metric of auto-

onomic nervous system sympathetic and parasympathetic balance) as an assessment of sleepiness in a sleep clinic population.

### 1.3. Information about ForSite™ Pupillometry [Figure 1]

The ForSite™ Pupillometer, NeuroOptics, (NeuroOptics Inc. 18101 Von Karman Avenue, Suite 1940, Irvine, CA, 92612 USA, [www.neuroptic.com](http://www.neuroptic.com)) is a hand-held portable, single button operated device measures pupil size, speed of reaction, and rate of constriction and dilation with autonomic changes. This instrument is suitable robust tool for measuring pupillary changes. Pupillometry was originally proposed by Lowenstein *et al.* in 1958, and has been used in a number of studies to evaluate somnolence in patients [6].

### 1.4. Design of Study

Prospective, controlled, cross-sectional study with correlation of objective and subjective measures of sleepiness.

## 2. Methods

Patients and control subjects were recruited from a sleep disorders and a general otolaryngology clinic at the Medical College of Wisconsin (MCW), Milwaukee, WI, USA and included patients with and without obstructive sleep apnea (OSA).

### Inclusion/Exclusion Criteria

We studied male and female patients of any ethnicity older than 18 years of age. Patients with a diagnosis of a primary autonomic neuropathy, who have undergone cataract surgery, have glaucoma, blindness in one or both eyes or recent history of head trauma (<6 months) excluded. Patients who are pregnant or have reasonable grounds to believe they are pregnant also excluded. All of the above can alter pupillary measures or affect the autonomic nervous system.

Following Internal Review Board (IRB) approval and after obtaining informed consent from all controls and subjects, Pupillometry (The ForSite™, NeuroOptics, Irvine, CA), was performed on 113 sleep clinic patients. All measurements (Maximum and minimum aperture, construction velocity, dilation velocity and latency) began with the right eye (R1) and subsequently alternated between eyes for a total of 6 measurements (e.g., R1, L1, R2, L2, R3, and L3). Complete pupillometric testing took approximately 5 minutes per patient.



Figure 1. The ForSite™ pupillometer.

Patient presented Constriction and dilation velocity and latencies, minimum and maximum aperture were obtained along with Epworth Sleepiness Score (ESS), 10 point Visual Analog Scale (VAS), BMI, gender, age and AHI. Three sets of measures were obtained and analyzed with ANOVA, t-test, Linear Regression and Pearson correlation coefficients (SAS, Cary, NC).

Mean Age 47 Years.

Mean Epworth score = 11.5.

Mean VAS score = 6.5.

### 3. Results

Both constriction velocity and constriction latency correlated with VAS ( $n = 88$ ,  $r = 0.28$ ,  $p = 0.007$  and  $r = 0.31$ ,  $p = 0.004$ ) [Figure 2]. Only constriction velocity correlated with AHI ( $n = 78$ ,  $r = -0.27$ ,  $p = 0.016$ ) [Figure 3]. Multivariate linear regression which include VAS and age predicted constriction velocity ( $r = 0.36$ ,  $p = 0.002$ ) [Figure 4] and latency ( $r = 0.38$ ,  $p = 0.001$ ). Using Pearson correlation, AHI and VAS combined were associated with constriction velocity ( $-0.273$  (0.016), and  $0.284$  (0.007), respectively) [Figure 5], [Table 1]. AHI vs Epworth  $R = 0.25$ ,  $p = 0.03$  [Figure 6]. Using a maximum constriction velocity threshold value (age adjusted) of 2.8,  $VAS \geq 6$  was predicted with a sensitivity of 83% and specificity of 84%.

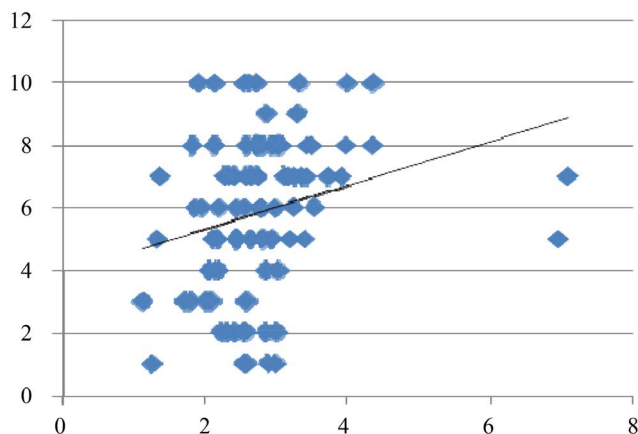


Figure 2. VAS vs. max pupillary constriction velocity ( $R = 0.28$ ,  $p = 0.01$ ).

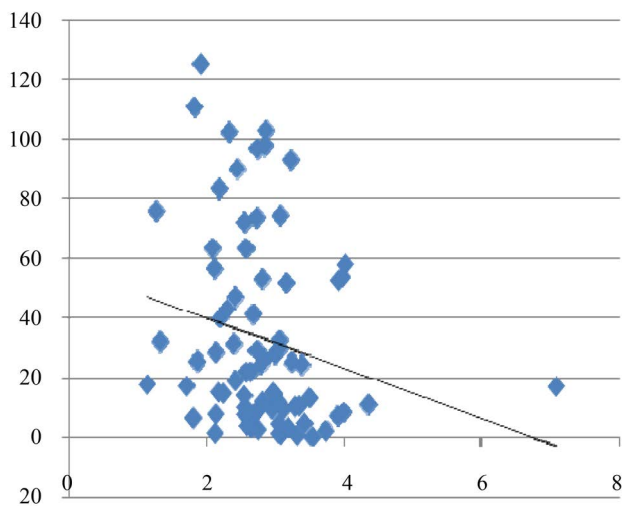


Figure 3. AHI vs. max pupillary constriction velocity ( $R = -0.27$ ,  $p = 0.02$ ).

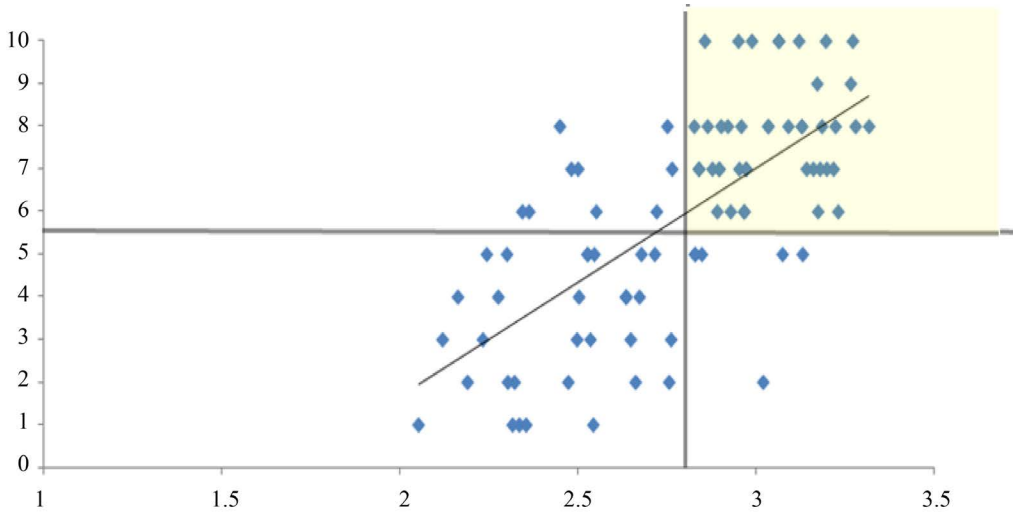


Figure 4. VAS vs. age adjusted max constriction velocity ( $R = 0.36$ ,  $p = 0.002$ ).

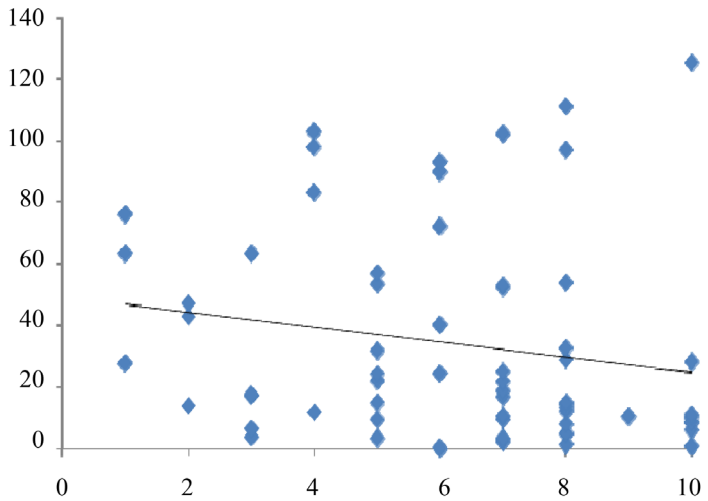


Figure 5. AHI vs. VAS ( $R = 0.18$ ,  $p = 0.15$ ).

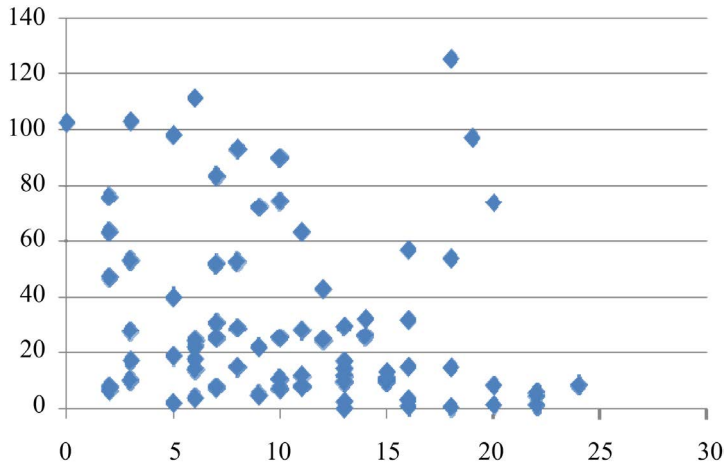


Figure 6. AHI vs. EPWORTH ( $R = 0.25$ ,  $p = 0.03$ ).

**Table 1.** Pearson correlation coefficients and descriptive statistics.

Variable 1	Variable 2	Correlation (p value)
<b>Maximum Pupillary Constriction Velocity</b>	Epworth	0.068 (0.487)
	Age	0.255 (0.025)
	<b>AHI</b>	<b>-0.273 (0.016)</b>
	<b>VAS</b>	<b>0.284 (0.007)</b>
Dilation Velocity	Epworth	0.136 (0.166)
	AHI	-0.0259 (0.823)
	VAS	0.107 (0.320)

#### 4. Discussion

Pupil response to light are under control of sympathetic and parasympathetic nervous system (autonomic nervous system), mydriasis by sympathetic and miosis by parasympathetic system. This device is an FDA Class I exempt device currently available for assessing pupillary function in patients with head trauma. The device consists of a disposable bracket that rests on the subject's forehead and cheek for stability. The subject focuses at a fixed distance (between 5 - 7 feet away) and does not blink for several seconds. The device emits a light causing the pupil to constrict. The device then measures the pupillary response at 40 frames per second. The device processes the data and reports on an LCD screen the maximum and minimum aperture, construction velocity, dilation velocity and latency of response.

Subjects are tested in a room with ambient light of 60 - 120 as determined by the device. The amount of light emitted from the device is approximately 125 microwatts with the irradiance of about 325 microwatts/cm<sup>2</sup> at the pupil. The LED light sources are 5 mm in diameter and are placed approximately 51 mm from the design plane of the pupil at an incline of about 16 degrees from the optical axis of the device. The duration of light pulse is 800 milliseconds.

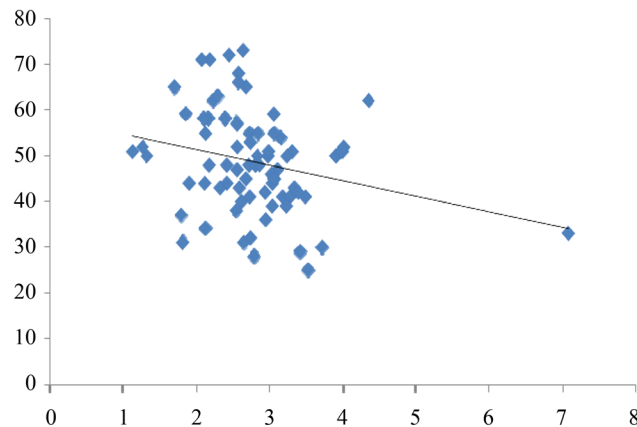
The velocities are calculated as a fit to the slope of the constriction and dilation phase of the pupil reflex. There is a nonlinear aspect to the fit of the constriction; however, this is in reality close to a linear fit most of the time. The fitting algorithms are applied to those segments of the pupillary light reflex which are demarked by the points of inflection which denote a change in direction. A sustained change (magnitude and direction) seen over at least 3 frames of data is required to validate an inflection point as being the onset of motion. Some articles in the literature report constriction velocity as the maximum speed observed in the constriction phase and likewise the latency reported is the time required to reach maximum velocity for initiation of the stimulus. The ForSite™ device uses the first sustained and verifiable movement in the calculations.

The scientific premise behind pupillometry is that pupil size and stability are inversely related to the degree of subjective sleepiness, normal pupil size is determined by the interaction between the parasympathetic and sympathetic nervous systems input to the muscles of the iris, the sphincter and the dilator, respectively. In a state of arousal there is increased sympathetic tone, resulting in mydriasis. Conversely in the state of drowsiness, there is predominance of parasympathetic tone, resulting in miosis.

Sleep-deprived individuals will demonstrate the inability to maintain their pupil size as evidenced by frequent pupillary oscillations during the testing period. A well-rested, alert subject is able to maintain a stable pupil size without oscillation in total darkness for 15 minutes [6]. Patients need to be free of any medications that may affect the parasympathetic or sympathetic pathways, to derive reliable results. A recent study demonstrated a strong relationship between ongoing sleep deprivation in normal subjects and typical changes in frequency profiles of spontaneous pupillary oscillations and the tendency toward instability of pupil size [7], with ongoing sleep deprivation, slow pupillary oscillations and Stanford Sleepiness Scale (SSS) scores significantly increased, whereas pupil diameter decreased significantly.

One study reported that the median values of most pupillometric variables in our sleepest patients (mean sleep latency less than 5 min) were significantly greater than those of well-rested normal volunteers. None of the variables was significantly different between mildly sleepy group of patients (latency >10 min) and the group of normal volunteers [8]. They further concluded that study suggests that there is a clear relationship between pupillometric variables and excessive daytime somnolence, as noted by Yoss and others [9]-[12].

There are limitation of our study such as more subjects may have increased power of study, our study was comparing measurement of sleepiness between objective measure (use of Pupillometer) to subjective measures (use of scales VAS and ESS), as discussed earlier these scales are subjective and has own limitations, based



**Figure 7.** Age vs. Max pupillary constriction velocity ( $R = 0.25$ ,  $p = 0.02$ ).

on patient perception of sleepiness and motivation, future study may use other objective measure of sleepiness such as MSLT instead subjective measures.

Our study supports the concept of using portable ambulatory pupillometry to identify individual at risk of abnormal sleepiness. Pupillometry measures of pupillary constriction velocity and constriction latency are both correlated to subjective sleepiness measured with a 10 point VAS. Pupillary constriction velocity was associated with sleepiness VAS [Figure 2], AHI [Figure 3], and age [Figure 7]. When corrected for age, pupillary constriction velocity successfully identified individuals with a VAS greater than 6. Pupillometry has the potential to be a rapid, widely available objective measure of sleepiness.

## 5. Conclusion

Pupillary constriction velocity and latency predict self-reported VAS state of sleepiness. While both are affected by age, only constriction velocity is affected by apnea severity. These data suggest that a portable pupillometer may provide a method to identify individuals with abnormal sleepiness, authors recommend further research with more subjects and use of pupillometer for assessing sleepiness and using objective method such as MSLT, instead subjective measures.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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