Diltiazem-Induced Vertical Eye-Movement Hypometria Detected by a High-speed Eye Tracking System Optimized for Clinical Investigation

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ABSTRACT

This paper discusses the optimization of a high-speed (1 kHz) 1st-Purkinje eye-tracking system for use in a clinical research setting. Through the use of stimulus generation and data analysis software, saccadic, pursuit, and fixation eye movements can be easily elicited, recorded, and analyzed in a clinical population. The system was used to investigate the effects of the *L*-type (slow) calcium channel blocker *diltiazem* on oculomotor performance in a single subject. Vertical saccades were found to have a significant decrease in accuracy (undershoot) ($p < 0.05$, one-way *ANOVA*). Increased variance was observed for gain and phase responses of pursuit movements. No significant changes were observed in central or 10° eccentric fixations. *L*-type calcium channels are found in high numbers (50-100-fold higher than in cardiac membranes) in skeletal muscle t-tubules, including those in extraocular muscle. We have shown the use of *diltiazem* to be associated, with a previously-unreported vertical eye movement hypometria.

INTRODUCTION

Eye-trackers optimized for various environments and applications have been developed at the *Institute of Biomedical Engineering* over the last 2 decades [1, 2, 3]. These range from high-speed, high-precision desk mounted systems, to ultra-light helmet-mounted, translation-insensitive devices. All systems are based on non-contact measurement approaches, and utilize low-level infrared illumination of the eye ($<800\,\mu W/cm^2$ at the cornea) [4]. Various ocular landmarks are imaged and detected, including the 1st Purkinje image, the bright and dark pupil, and a number of combinations of these. All systems share the need for a common user interface [5, 6] and require specialized stimulus generation. One of these systems has been optimized for use in a clinical environment where measurement of perturbed CNS function associated with dementia and the use of drugs is the research focus [7].

EYE-MOVEMENT ANALYSIS

We developed a generic test battery and associated numerical analysis techniques to facilitate investigation of oculomotor performance in such a clinical setting. Stimulus routines run in association with existing data acquisition and management software, previously described [5]. Saccadic, pursuit, and fixation eye movements are elicited, recorded on removable hard disk cartridges, and analyzed off-line. A typical eye movement sequence from a 5-minute experiment generates some 1.2 mB of data.

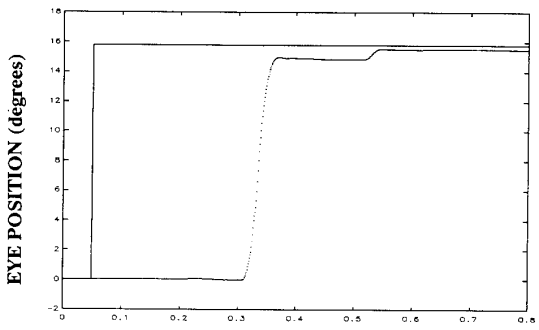

Figure 1. *The solid trace indicates a transition of the visual stimulus to the right approximately 16°, at relative time 50 ms. The lower trace is the saccadic response after a 250 ms delay. The eye moves rapidly to approximate the target, and then makes a secondary corrective movement. The dots (which can only be seen when the eye is moving rapidly) represent eye position estimates which occur every ms.*

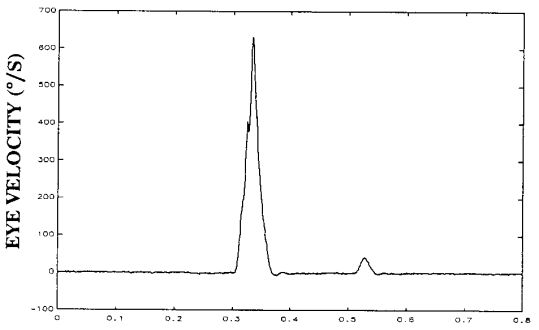

Figure 2. *Velocity plot derived from Figure 1. The primary saccadic velocity exceeds 600°/S; the corrective saccade peaks at less than 50°/S.*

Saccades of any amplitude and direction compatible with the stimulus device and the eye tracker range (±25° horizontal; ±15° vertical, in this case) may be generated, with equal or selected frequencies of occurrence. Analysis is automated and includes measurement of latency, instantaneous and peak velocity, and accuracy of each saccade with respect to target movement (Figures 1 & 2). For each session, parameters are estimated to fit the data to the standard main-sequence for duration/peak-velocity *vs* amplitude [8]. These data are available for standard statistical analysis by such programs as *BMDP, SAS*, or *SPSS*.

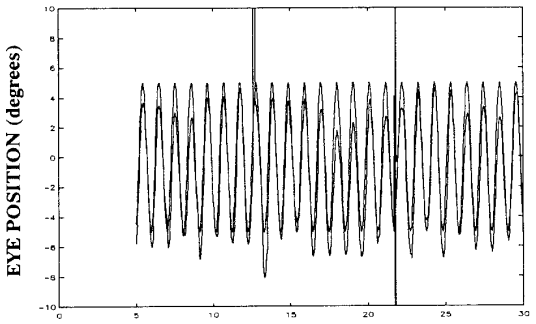

Figure 3. *The trace of constant amplitude represents the visual stimulus (0.96 Hz). The trace of varying amplitude is the following eye's response. The 2 vertical lines at approximately 13 and 22 seconds are eye blinks.*

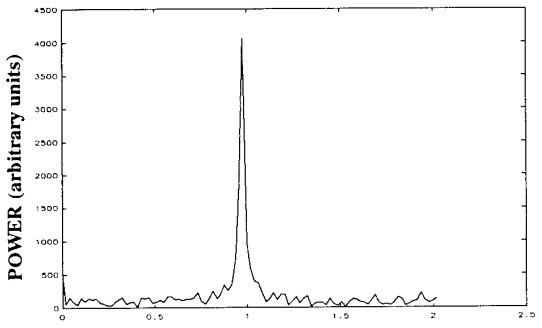

Figure 4. *FFT power spectrum of the eye's response in Figure 3.*

The **pursuit** paradigm involves tracking a target which moves in a circular trajectory with a fixed radius centered on the *primary position* (in which the head is held vertical, and the eyes look straight ahead).

Different target velocities are generated by altering the angular velocity of the target. Multiple target velocities, and radii of eccentricity, usually in the range of 5-50°/S at a 5° - 10° radius are recorded. Each recording is long enough (60 S) to allow off-line spectral analysis with a resolution of 0.05 Hz. *Fourier* analysis is used to calculate magnitude and phase of both stimulus and response, from which gain and relative phase are calculated. A specific advantage of *Fourier* analysis is its ability to separate energy associated with data artifacts, and non-pursuit movements, from actual response energy. The problems associated with aliasing and windowing of data are also dealt with explicitly. Other measures such as mean-square tracking-error are incorporated.

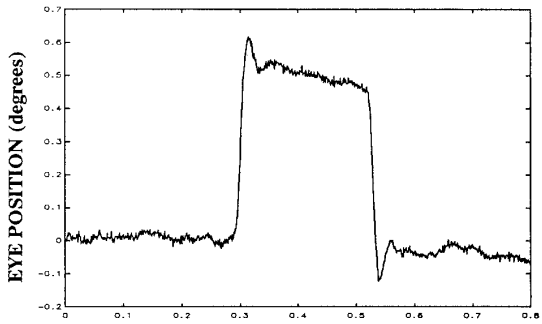

Figure 5. *A typical fixation eye movement sequence. The up-going microsaccade is less than 0.7° in peak amplitude. Note the drift following this first movement, and the second, down-going, microsaccade. Both microsaccades demonstrate small amounts of over-shoot.*

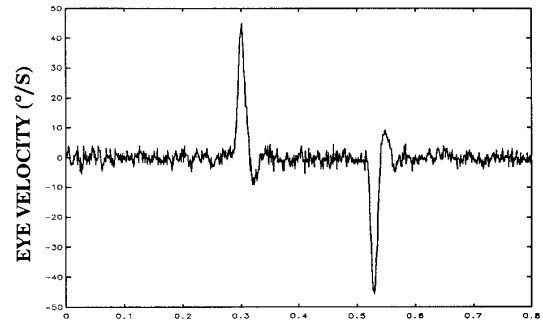

Figure 6. *The velocity profile of the microsaccades shown in Figure 5.*

Fixations are generated for the primary position, and any eccentric positions which are hardware compatible. Data collected are analyzed for stability of fixation, frequency of micro-saccades, drift, and ocular tremor. Measurement of ocular tremor again utilizes *Fourier* analysis. The data collection and analysis techniques described provide an abundant source of

data which quantify oculomotor function for the clinical investigator, in a standardized manner.

EXPERIMENTAL METHOD

To demonstrate the utility of this system, an individual was studied intensively under the acute effects of the drug *diltiazem* [9]. While the effects of this *L*-type (slow) calcium channel blocker are largely confined to cardiac and vascular smooth muscle, rare instances of *drowsiness*, *dizziness*, and *vertical diplopia* have been reported. A recent investigation showed *in vitro* and *in vivo* effects on rabbit extraocular muscle [10]. To examine the ocular effects of *diltiazem*, the eye movements of an otherwise-healthy 48-year old male patient about to be placed on *diltiazem* for treatment of modest hypertension (145/95 mmHg) were characterized before and during therapy with *diltiazem* 180 mg/day.

Eye movements were measured in a desk-mounted, bite-plate-stabilized 1st-Purkinje system with a spatial resolution of 20 arc seconds, and a temporal resolution of 1 ms [2, 3]. The stimulus battery consisted of constant-velocity circular pursuits (5, 10, 15, 20, 30, 40, and 50°/S clockwise-moving, 1 mm point target at 5° radius around the primary position); saccades (2° - 20° horizontal and vertical); and, 60-second fixations (primary position, and at 10° eccentricities). Measurements were taken in the morning on three successive days before drug therapy, daily during the 1st week of therapy, and at 3 weeks after therapy began.

SUMMARY OF RESULTS

Vertical saccades were found to have a significant ($p < 0.05$, one-way *ANOVA*) difference in accuracy (hypometria) between the pre- and post-drug conditions. Gain and phase responses were determined for both the vertical and horizontal components of the circular pursuits: while no significant changes in these parameters were observed, variance in parameters between pre- and post-drug was seen to increase. *L*-type calcium channels are found in high numbers (50-100-fold higher than in cardiac membranes) in skeletal muscle *t-tubules*, including those in extraocular muscle. We have shown the use of *diltiazem* to be associated, in one subject, with a previously-unreported vertical eye movement hypometria.

DISCUSSION

These clinical results are consistent with quite recently reported effects of *diltiazem* in rabbit extraocular muscle [10]. Jacoby *et al.* (1989) found that this drug reduced the contractility of extraocular muscles by reducing the sustained tension that is generated by the tonic, multiply-innervated fibers, and that it decreased the resting tension of the muscle. Direct *in vivo* injection into the extraocular muscle produced a temporary weakening, and deviation of eye position. These authors speculate that *diltiazem* might be an alternative to strabismus surgery.

CONCLUSION

The eye tracking system described has proven valuable and reliable in the conduct of clinical trials in which it is desired to assess oculomotor function. It is presently deployed in an investigation of the effects of acute nicotine withdrawal in dependent smokers [7], and in a study to detect early, reversible alcohol-induced brain damage.

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