Published in final edited form as:

J Glaucoma. 2018 May ; 27(5): 429–432. doi:10.1097/IJG.0000000000000898.

Neuro-Vascular Changes associated with the Water Drinking Test

Gustavo Gameiro, BS¹, Pedro Monsalve, MD¹, Iuri Golubev, MD¹, Lori Ventura, MD¹, and Vittorio Porciatti, DSc¹

¹Bascom Palmer Eye Institute, University of Miami Miller School of Medicine

Abstract

Purpose—The Water Drinking Test (WDT) is currently used to temporarily elevate intraocular pressure (IOP) and predict peak IOP in glaucoma. This study investigates neurovascular changes associated with WDT in normal subjects.

Methods—The effect of WDT (1 liter in 5 minutes) on IOP, mean brachial blood pressure (MAP), heart rate (HR), and pattern electroretinogram (PERG) was assessed within the next hour in 16 healthy subjects (mean age 33.5 ± 7.9 years). As a control, testing was repeated in the same subjects without WDT one week later.

Results—Compared to control, WDT resulted in significant peak changes of the following parameters compared to baseline: IOP: $+1.7 \pm 1.8$ mm Hg after 30', MAP: $+3.9 \pm 6.3$ mm Hg after 15'; HR: -9.2 ± 9.8 bpm after 15', PERG latency: $+2.1 \pm 0.9$ ms after 15'.

Conclusions—In addition to IOP elevation, WDT was associated with significant changes of hemodynamic parameters and retinal ganglion cell function in young healthy subjects. As these represent risk factors for glaucoma, their assessment upon WDT might increase its predictive power for glaucoma development.

Keywords

water drinking; intraocular pressure; systemic blood pressure; retinal ganglion cell function; pattern electroretinogram

Introduction

The Water Drinking Test (WDT) consists of drinking a substantial volume of water over a short period, which causes a temporary elevation of the intraocular pressure (IOP) [1–4]. After receiving substantial interest as a diagnostic test for glaucoma, the WDT is currently considered having insufficient sensitivity and specificity for glaucoma diagnosis. A new wave of interest for the WDT has been recently generated to predict nighttime peak IOP and associated likelihood of progression [1–4].

Address for correspondence: Vittorio Porciatti D.Sc. Bascom Palmer Eye Institute, 1638 NW 10th Ave., Room 507C, Miami, FL, 33136, vporciatti@med.miami.edu, Tel: 305-326-6050; Fax: 305-482-5093.

Financial disclosure: GG, none; PM, none; IG, none; LV, none; VP, none.

The physiology of WDT is not well understood. Here we show that, in addition to IOP elevation, WDT alters several hemodynamic parameters and retinal ganglion cell function as measured by Pattern Electroretinogram (PERG).

Methods

Subjects

Study subjects were 16 healthy subjects (mean age 33.5 ± 7.9 years) with normal vision (Snellen BCVA 20/20, refractive errors range -2.5 to $+1.5$ diopters). WDT consisted on drinking 1 liter of bottled water at room temperature within 5 minutes [5]. Study outcome measures were IOP (Reichert PT-100), time-integrated mean brachial blood pressure [$\text{MAP} = \text{Diastolic} + 0.42 \times (\text{Systolic} - \text{Diastolic})$] [6,7], heart rate (HR), (Welch-Allyn Vital Signs Monitor 300 series), and steady state pattern electroretinogram (PERG, Jorvec Corp) [8], which were assessed before WDT and every 15 minutes thereafter over one hour. The same protocol was repeated in the same subjects without WDT (Control) in a different session about one week thereafter. The study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Miami. Informed written consent was obtained from all subjects.

PERG method

The PERG was recorded using a commercially available instrument (Jorvec Corp, Miami, FL) as summarized in the example of Figure 1. The visual stimulus consisted of a black-white horizontal grating (1.6 cycles/deg, 15.63 reversals/s, 98% contrast, 800 cd/sqm mean luminance) generated on a Light-Emitted-Display (LED) (14×14 cm), which was presented binocularly at 30 cm viewing distance in a dimly lit room. Subjects in a seated position wore corrective lenses as needed for the 30-cm viewing distance. All subjects had a Jaeger score J1+ in each eye. Steady-state PERG signals were simultaneously recorded from both eyes using skin electrodes (Grass Technologies, West Warwick, RI) over the lower eyelids (reference ipsilateral temple, ground central forehead), amplified ($100,000 \times$) filtered (1–300 Hz), and averaged over 1,024 epochs in sync with the contrast reversal automatically rejecting epochs occasionally contaminated by blink artifacts. Noise signals were simultaneously retrieved using the $\pm$ reference method [9]. Recording time of 1,024 artifact-free epochs was approximately 2.2 minutes depending on the number of rejected epochs. PERG waveforms were Fourier analyzed to isolate the frequency component at the reversal rate (15.63 Hz) whose amplitude (μV) and phase (degrees) were evaluated. Phase values were converted in latency (ms), which corresponded to the time-to-peak of the positive wave of the PERG waveform [8]. This also corresponds to the peak-latency of the P50 waveform component of the standard transient PERG [10]. Noise signals had a very small amplitude (mean $0.08 \mu\text{V}$) across conditions and will not be further discussed. Further details are reported elsewhere [8].

Statistics

Generalized Estimating Equation (GEE) analysis was used to assess the effects of WDT and elapsed time of measurement on each of the variables. For ocular variables, an exchangeable correlation matrix was used to account for the correlation between two eyes of the same

subject. For each variable, an analysis was performed to test the difference between WDT and control measurements at baseline. Then a second analysis was done to evaluate whether there was a statistical interaction between WDT (vs control) and the time course of the five measurements from baseline to 60 minutes.

Results

Figure 2 summarizes the average change over time (5 consecutive measurements in 15' steps) of IOP, hemodynamic parameters and PERG under control (no-WDT) and test (WDT) conditions. For the WDT condition, time zero represents baseline before WDT. Results of GEE statistical analysis are summarized in Table 1. At baseline, control and WDT conditions had overlapping values for HR, MAP, IOP, OPP, and PERG latency (all $P > 0.30$); however, each of these variables demonstrated a different time course for control and WDT conditions (all $P = 0.014$, test of WDT $\times$ Time interaction). In control condition, HR tended to decrease over time ($P < 0.01$). Compared to control condition, however, HR in WDT condition displayed a sharp decrease at the 15' time point (69.9 ± 8.0 vs. 60.7 ± 9.0 bpm, $P = 0.0019$) and remained significantly lower for all the test period (interaction WDT $\times$ time, $P < 0.001$). Compared to control condition, MAP in WDT condition displayed a significant increase at the 15' time point (94.5 ± 9.2 vs. 98.4 ± 8.5 mm Hg, $P = 0.027$) and then tended to remain higher than baseline (interaction WDT $\times$ time, $P < 0.001$). IOP increased upon WDT with a broad maximum at the 30' time point (17.23 ± 2.6 vs. 18.91 ± 3.0 mm Hg, $P = 0.0017$) and slowly recovered control values at the 60' time point (interaction WDT $\times$ time, $P < 0.001$). PERG latency significantly increased compared to baseline with a maximum at the 15' time point (52.01 ± 1.9 vs. 53.49 ± 2.38 ms, $P = 0.0002$) and then slowly recovered control values at the 60' time point (interaction WDT $\times$ time, $P = 0.002$). OPP displayed a significant WDT $\times$ time interaction ($P = 0.014$), but the absolute changes from baseline were modest. Baseline PERG amplitude was modestly elevated under WDT condition compared to control condition ($P = 0.037$) and this difference remained significant over the post baseline time points ($P = 0.038$, test of main effect over all time points). Yet, none of the differences from baseline were statistically significant between the WDT and control measurements (all $P > 0.12$). There was also a marginally significant WDT $\times$ time interaction ($P = 0.046$), and be explainable, in whole or in part, by multiple testing artifact. Altogether, data presented in figure 2 show that WDT had a significant, substantial effect on IOP, hemodynamic parameters (HR, MAP) and PERG latency, apparently with a faster time course for neurovascular parameters compared to IOP.

Discussion

The current purposes of WDT-induced IOP elevation are to identify peaks that correlate with circadian peaks, risk assessment for progression [4], and evaluation of efficacy of treatment [11]. In addition to induce IOP elevation, the present study showed WDT-induced hemodynamic changes [1–4,12,13] and PERG changes. The PERG latency was significantly delayed 15' after WDT, and progressively recovered pre-WDT baseline conditions over one hour. The temporal dynamics of PERG latency changes paralleled that of HR decline and MAP elevation. In contrast, the temporal dynamics of IOP elevation appeared to follow a slower time course with a broad maximum 30' after WDT. The physiological relationship

between PERG and hemodynamic variables is complex. WDT is associated with hypervolemia that may cause a rise of blood pressure and stroke volume [12,14]. The cardiac output (heart rate $\times$ stroke volume) was not expected to change substantially, as the drop in heart rate should have been compensated by the increase in stroke volume. The estimated OPP had only modest changes after WDT. WDT also may have caused hemodilution, resulting in hyposmolality and hyponatremia [12,13,15]. Hyponatremia after excessive water drinking is known to cause confusion, lethargy, and even epilepsy and death in extreme cases [16]. The ERG is known to be very sensitive to reduction of sodium concentration [17]. It is possible that WDT-induced hyponatremia, together with other unknown factors, caused transient delay of PERG latency, which is considered expression of slowed down RGC electrical activity [18]. That RGC function was transiently altered with WDT is consistent with several studies reporting severe brain dysfunction after excessive water drinking [16].

Altogether, this study extends previous reports on WDT emphasizing its transient neurovascular effects in addition to IOP elevation. In particular, PERG latency was significantly delayed. Although the study was conducted in healthy subjects, it is plausible that the PERG changes could have been of greater magnitude in glaucomatous eyes, therefore suggesting its utility as a stress test for RGC function and hence potential application for risk assessment. In principle, assessing PERG changes after WDT might also offer the opportunity to test the protective effects of medications on transiently-induced RGC dysfunction.

Acknowledgments

Financial support: NIH-NEI RO1 EY014957, NIH center grant P30-EY014801, unrestricted grant to Bascom Palmer Eye Institute from Research to Prevent Blindness, Inc.

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Figure 1.

Set up for the PERG method. A: LED tablet displaying a horizontal grating (98% contrast, 800 cd/sqm, 14 × 14 cm size). For PERG recording, the grating reversed in contrast 15.63 times/s. B: subjects looked at the center of the display for 2 minutes from 30 cm distance with natural pupils and blinking, while signals were acquired from skin electrodes taped on the lower eyelids. C: Examples of PERG waveforms (thick lines) recorded simultaneously from each eye together with corresponding noise waveforms. For both PERG and noise, the sinusoidal component at the reversal rate (dashed lines) was isolated with Fourier analysis and its zero-to-peak amplitude (vertical arrow), phase, and time-to-peak latency (horizontal arrow) automatically assessed

Figure 2.

Effect of WDT on heart rate (HR), mean brachial pressure (MAP), intraocular pressure (IOP), estimated ocular perfusion pressure (OPP), PERG amplitude, and PERG latency. In all panels, open symbols represent the mean values ($\pm$ SEM) before (time zero) and at different times after WDT. Closed symbols represent corresponding values in the same subjects without WDT. Asterisks represent significance levels compared to baseline established with GEE analysis (*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$, $N = 16$).

Table 1

Statistical GEE analysis

Measure	Controls over time GEE P-value	Controls vs. WDT, Baseline difference GEE P-value	Interaction WDT vs. Means, GEE P-value
HR	<0.001 (0> 45', 60')	0.937	<0.001
MAP	0.176	0.861	<0.001
IOP	0.404	0.358	<0.001
OPP	0.081	0.890	0.014
PERG_amplitude	0.234	0.037	0.046
PERG_latency	0.822	0.312	0.002