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*Original article*

# Correlation and agreement between the 24-hour diurnal tension curve, the water-drinking test, and the postural-change test in glaucoma patients*

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## Abstract

*Aim:* To investigate whether the water-drinking test (WDT) and the postural-change test (PCT) can predict the 24-hour diurnal tensional curve (DTC) intraocular pressure (IOP) peak and fluctuation by assessing the correlation and agreement between these three tests in medically treated primary open-angle glaucoma (POAG) patients.
*Methods:* 18 POAG patients underwent the DTC, WDT, and PCT. Pearson's correlation coefficient and Bland-Altman plots were used to assess the correlation and agreement between the results, respectively.
*Results:* Mean DTC IOP peak was 18.72 ± 4.31 mmHg and mean DTC IOP fluctuation was 7.00 ± 2.54 mmHg. The IOP peak was outside office hours in 50% of the subjects. We observed poor correlations between the DTC and WDT fluctuations, and the DTC and PCT fluctuations (r = -0.125, P = 0.619; r = 0.349, P = 0.155, respectively). There was a moderate positive correlation between the DTC and WDT peaks (r = 0.493, P = 0.03) and a strong positive correlation between the DTC and PCT peaks (r = 0.722, P < 0.001). However, Bland-Altman plots demonstrated poor agreement among IOP peaks and fluctuations between the three tests. WDT and DTC IOP peaks differed by

*The water-drinking test and the postural-change test should be used with caution to estimate peak IOP.

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2 mmHg or more in 56% of the measurements. PCT and DTC IOP peaks showed that 83% of the measurements had differences greater than 2 mmHg.
*Conclusions:* Despite moderate to strong correlations between DCT and WDT peaks and DTC and PCT IOP peaks, the agreement was generally poor, suggesting that they should be used with caution to estimate peak IOP.

*Keywords:* intraocular pressure (IOP), water/drinking test (WDT), diurnal IOP, postural-change test (PCT)

## 1. Introduction

Intraocular pressure (IOP) is the main risk factor for the development and progression of glaucoma.[1] IOP is not constant throughout the day, with nocturnal IOP in the supine position being higher than diurnal IOP in the sitting position.[2-5] Both peak IOP and diurnal IOP fluctuation have been reported to be risk factors for the development and progression of the disease.[6,7]

IOP peaks have been related to the progression of visual field defects, but 30-50% of patients may not have their IOP peak detected during routine office hours,[7-10] thus emphasizing the value of 24-hour IOP monitoring in the management of glaucoma patients.[5,11] The 24-hour diurnal tensional curve (DTC) in the habitual position, which includes IOP measurements every three hours in the sitting (during the day) and supine positions (at night), is the gold standard method used to determine peak IOP and IOP fluctuation. However, the DTC may be inconvenient and troublesome for both patients and doctors, since it generally demands hospital admission.

Several methods have been designed to predict peak IOP and diurnal IOP fluctuation. The water-drinking test (WDT) is a provocative test designed to estimate the outflow facility reserve of the eye.[10,12] It was first used as a tool for glaucoma diagnosis, and subsequently to estimate the severity and risk of progression in glaucoma patients.[9] It has been suggested that the WDT is capable of predicting IOP peak during the DTC.[5,8,9,12-15]

The postural-change test (PCT) evaluates the IOP increase that follows a shift from upright to horizontal position,[5,16,17] possibly due to choroidal congestion and episcleral venous hypertension.[16,17] It has been suggested that this test reproduces the physiological increase in IOP observed during the night in the supine position.[17,18] The IOP increase in the PCT has been reported to be around 4.6 ± 2.6 mmHg.[5]

A number of previous studies have investigated the correlation between IOP peaks measured with the DTC, the WDT and the PCT,[6,9,14] others have evaluated the agreement between modified DTCs and the alternative tests,[11,16] but none have actually analyzed the agreement between these measurements and a complete 24-hour DTC. The purpose of this study was to investigate whether the WDT and PCT can in fact predict the 24-hour DTC peak and fluctuation by assessing the

agreement between these three tests in medically treated primary open-angle glaucoma (POAG) patients.

## 2. Methods

The study was approved by the Ethics Committee of the State University of Campinas and adhered to the tenets of the Declaration of Helsinki. Between September and November 2014, 18 consecutive medically treated POAG patients, who were followed at the Glaucoma Service of the University of Campinas, Brazil, were recruited. Written informed consent was obtained from each participant.

Individuals with POAG were defined as having a history of IOP ≥ 21 mmHg in three distinct visits before the onset of treatment, open angle at gonioscopy, abnormal optic discs with signs of glaucomatous neuropathy, and repeatable abnormal visual fields with typical glaucomatous defects, determined by Anderson's criteria.[19] Glaucomatous optic neuropathy was defined as the presence of at least two of the following characteristics: a localized optic disc neuroretinal rim defect, cup-to-disc ratio (C/D) > 0.6, disc hemorrhage, peripapillary nerve fiber layer defect, or cup asymmetry between the eyes of 0.2 or more. Patients with early glaucomatous changes, defined as mean deviation (MD) > -6 dB in at least one eye, and patients using up to two hypotensive medications were eligible for this study.

Individuals who had undergone previous intraocular surgery (except for uneventful phacoemulsification) or laser procedures, or those with a history of angle-closure glaucoma, secondary glaucoma, trauma, or eye inflammation were not included in this study. Women who were pregnant or breastfeeding were also excluded.

Each patient underwent a complete ophthalmologic examination, which included best-corrected visual acuity (BCVA), slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundus examination, and automated achromatic perimetry (24-2 program, SITA Standard Strategy, Humphrey Field Analyzer 740, Zeiss, Dublin, CA, USA).

Patients were then admitted to the Ophthalmology Infirmary at the Hospital de Clinicas of the University of Campinas. They were told to keep using their medication drops at the same routine hours.

### 2.1. Diurnal tensional curve (DTC)

During the DTC, IOP measurements were recorded with a Goldmann applanation tonometer (GAT; Haag Streit, Koeniz, Switzerland) every three hours in the sitting position during daytime (from 9 AM to 9 PM), and in the supine position with a Perkins tonometer (Haag Streit, Koeniz, Switzerland) during the nocturnal period (from midnight to 6 AM). All measurements began at 3 PM. IOP was measured by one of two experienced ophthalmologists. Both the GAT and Perkins tonometers were

calibrated and tested to produce reliable measurements. Peak IOP was defined as the highest IOP measured over the 24-hour period, whereas IOP fluctuation was defined as the difference between the highest and lowest IOP measured over the 24-hour period.

### 2.2. Water-drinking test (WDT)

The WDT was performed while patients were hospitalized, beginning right after they had their last IOP measurement recorded for the DTC at noon. Subjects were asked to drink 1 L of water in 5 minutes, and IOP measurements were made every 15 minutes for 1 hour thereafter with GAT. The WDT peak was defined as the highest IOP measured during the test, and the WDT fluctuation was defined as the difference between the WDT peak and IOP at the beginning of the test. Patients were asked to fast for at least 4 hours before undergoing the WDT.

### 2.3. Postural-change test (PCT)

The PCT was also performed while patients were hospitalized. After the 9 AM measurement (in the sitting position), subjects were asked to go back to their room and remain in the supine position for 30 minutes. Measurements were then made with the Perkins tonometer. Postural IOP fluctuation was defined as the difference between IOP measurements in the sitting and supine positions.

### 2.4. Statistical analysis

The study was designed to have a power of 80% to detect an IOP difference of 2 mmHg between tests, considering a 2 mmHg standard deviation. The target sample size was 18 eyes (18 subjects). Only the right eye was selected for analysis. Statistical analysis was performed using platform R 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria). Demographic and clinical data, including age, gender, height, weight, body mass index (BMI), central corneal thickness (CCT), mean deviation, and cup-to-disc ratio were tabulated.

IOP peak and IOP fluctuation in each test were compared using the paired Student's t-test. The Pearson correlation coefficient and Bland-Altman plot were used to determine the correlation and agreement between results, respectively. The Pearson correlation coefficient is a numerical value (r) that ranges from -1 (maximum negative correlation) to 1 (maximum positive correlation), where 0 represents no correlation. The correlation can be described as weak if r falls between 0.10 and 0.30, moderate if r is between 0.31 and 0.50, and strong if r is 0.51–1.00.[20] P values < 0.05 were considered statistically significant.

The Bland-Altman plot of agreement between two methods is determined using the differences between the values obtained by the two methods (y axis) vs the mean of the two measurements (x axis). The 95% limit of agreement, calculated as the mean difference ± 1.96 standard deviation, provides an interval where 95% of the differences between measurements are expected to lie.[21]

*Table 1*. Baseline characteristics of all patients (n = 18)

| Characteristic | Mean ± SD |
|---|---|
| Age (years) | 70.33 ± 6.62 |
| Sex | |
| Male | 8 |
| Female | 10 |
| BMI (Kg/m$^2$) | 28.74 ± 4.08 |
| CCT (μm) | 537.33 ± 12.47 |
| MD (dB) | -5.6 ± 4.67 |
| Vert C/D | 0.69 ± 0.18 |
| Baseline IOP (mmHg) | 16.86 ± 2.84 |
| Medications (number) | 1.22 ± 0.80 |

MD: mean deviation BMI: body mass index C/D: cup-to-disc

## 3. Results

This was a prospective intervention study involving 18 POAG patients (18 eyes). Subject baseline characteristics are shown in Table 1. Baseline IOP was defined as the subjects' mean IOP in their last three visits.

### 3.1. DTC results

The mean DTC IOP was 14.88 ± 3.34 mmHg, mean DTC IOP peak was 18.72 ± 4.31 mmHg, and mean DTC fluctuation was 7.00 ± 2.54 mmHg. The peak IOP occurred outside office hours (between 9 PM and 6 AM) in 50% (n = 9) of the subjects, with all of them occurring between midnight and 6 AM.

### 3.2. WDT results

The mean WDT peak was 19.0 ± 4.56 mmHg and the mean WDT fluctuation was 5.11 ± 2.76 mmHg. The mean DTC IOP peak and fluctuation were not significantly different from those measured by the WDT (P = 0.79 and P = 0.06, respectively).

### 3.3. PCT results

The mean PCT peak was 14.11 ± 3.41 mmHg, and the mean PCT fluctuation was 0.61 ± 1.72 mmHg. The mean DTC IOP peak and fluctuation were significantly different from those measured by the PCT (P < 0.001).

### 3.4. Interpretation

We observed poor correlations between the DTC and WDT fluctuations and the DTC and PCT fluctuations (r = -0.125, P = 0.619; and r = 0.349, P = 0.155, respectively).

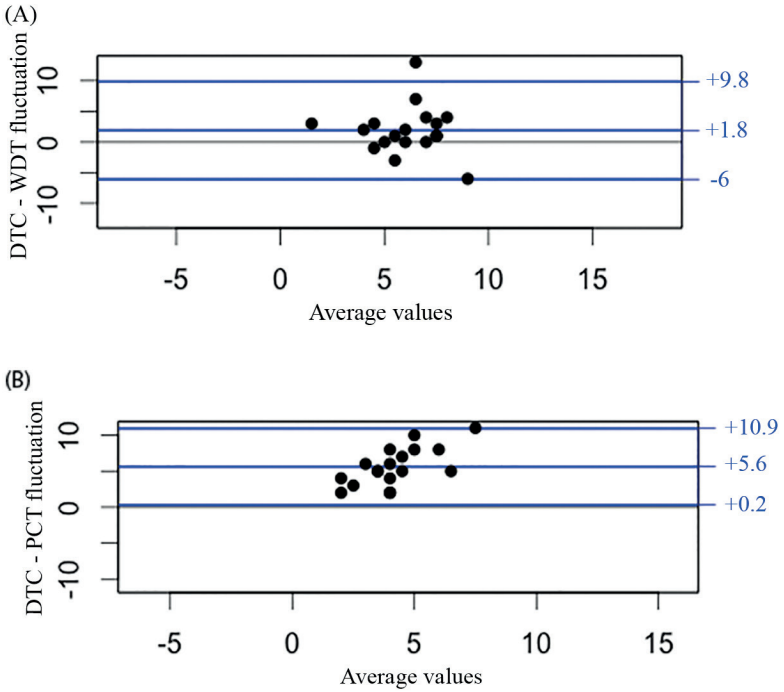


*Fig. 1.* Bland-Altman plots. Three lines are displayed. The thick line represents the mean difference of IOP fluctuation between the two tests. The upper and lower dash lines represent the 95% limit of agreement (± 1.96 SD). (*A*) Bland-Altman plot of DTC and WDT IOP fluctuation. (*B*) Bland-Altman plot of DTC and PCT IOP fluctuation.

The Bland-Altman plot comparing the WDT and PCT IOP fluctuations (Fig. 1A) shows that the mean IOP fluctuation difference between the two tests was 1.8 mmHg, and that the 95% limit of agreement between the two tests ranged from -6.0 to 9.8 mmHg. Fifty-percent of the eyes had IOP fluctuation differences greater than 2 mmHg. The Bland-Altman plot comparing the DTC and PCT IOP fluctuations (Fig. 1B) shows that the mean IOP fluctuation difference between the two tests was 5.6 mmHg, and that the 95% limit of agreement between the two tests ranged from 0.2 to 10.9 mmHg. IOP fluctuation differences were greater than 2 mmHg in 88.9% of the eyes.

There was a moderate positive correlation between the DTC and WDT peaks ($r = 0.493$; $P = 0.03$, Fig. 2) and a strong positive correlation between the DTC and PCT peaks ($r = 0.722$; $P < 0.001$, Fig. 3). However, the Bland-Altman plots demonstrated poor agreement between the IOP peak measurements obtained with the three methods. The Bland-Altman plot comparing the DTC and WDT peaks (Fig. 4A) shows that the mean difference of peaks between the two tests was 0.2 mmHg,

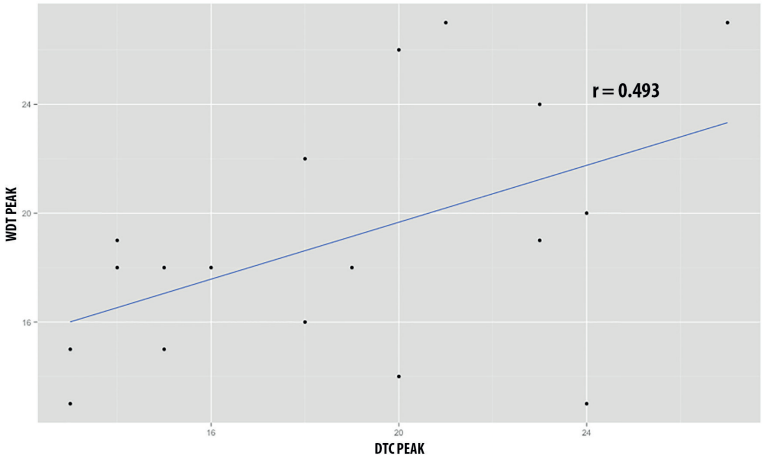


*Fig. 2.* Correlation between the DTC and WDT peaks.

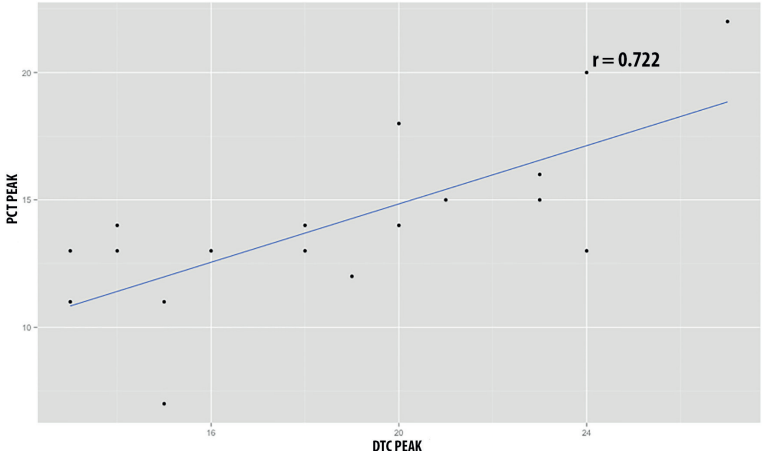


*Fig. 3.* Correlation between the DTC and PCT peaks.

and that the 95% limit of agreement between the two tests ranged from -9.2 to 8.6 mmHg. Furthermore, 56% of the measurements had IOP peak differences greater than 2 mmHg.

The Bland-Altman plot comparing the DTC and PCT IOP peaks (Fig. 4B) shows that the mean difference of peaks between the two tests was 4.61 mmHg, and that the 95% limit of agreement between the two tests ranged from -1.3 to 10.5 mmHg. Furthermore, 83% of the eyes had peak differences greater than 2 mmHg.

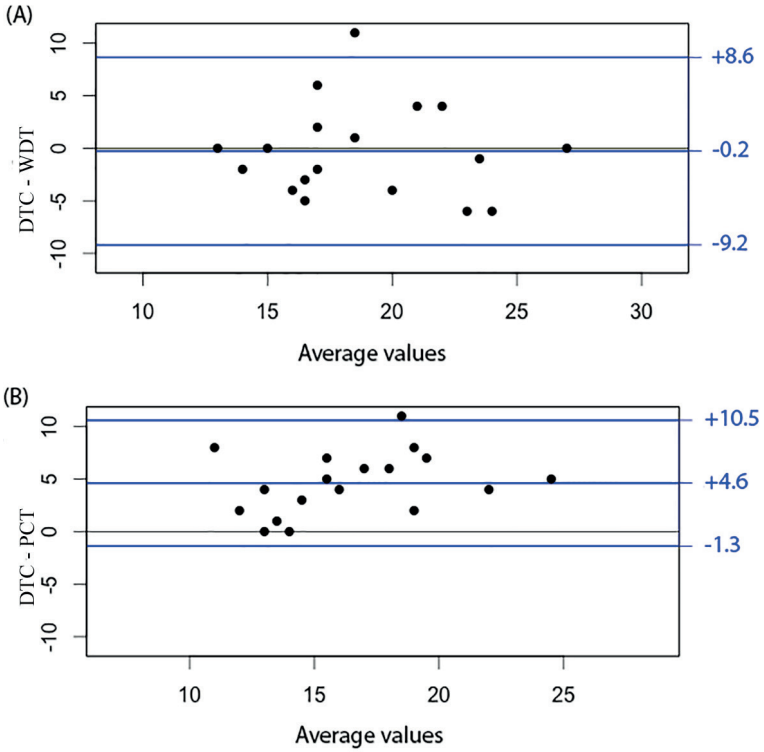


*Fig. 4.* (*A*) Bland-Altman plot of DTC and WDT IOP peaks. (*B*) Bland-Altman plot of the DTC and PCT IOP peaks.

## 4. Discussion

Mean IOP, peak IOP and IOP fluctuation are important risk factors for the development and progression of glaucoma.[2,3,6] As mentioned before, the 24-hour DTC is the current gold standard to assess IOP characteristics throughout the day, but it is time-consuming and impractical. In fact, our study confirms that 50% of IOP peaks measured during the 24-hour DTC would not be detected during office hours. Attempts have been made to develop an alternative test capable of providing information regarding the behavior of IOP throughout the day, especially about IOP peak and fluctuations. However, most of the studies that compare IOP peak and fluctuation obtained with the DCT and the alternative methods rely on correlation, not agreement analysis.[5,13,15,16]

The Pearson coefficient measures linear correlation rather than agreement. Methods can correlate well yet disagree greatly, as would occur if one method read

consistently higher than the other. Correlation typically depends on the range of the measures being assessed, with wider ranges often resulting in stronger correlations, but not as a consequence of better agreement between the methods.[21]

When the intention is to evaluate the agreement between two methods that measure the same quantity, it is important to properly use Bland-Altman plots, including the analysis of limits of agreement, and to comment on whether these limits are clinically acceptable. It is also important to assess two aspects of agreement: how well the methods agree on average and how well the measurements agree for individuals.[21]

The PCT is a provocative test that relies on the IOP change that occurs with modifications in both body and head positions. The majority of the available studies in the literature analyzed the difference in IOP values between the sitting and supine positions.[4,18] It has been proposed that the immediate increase in IOP upon lying down may be due to a sudden increase in uveal blood flow, leading to increased aqueous production and also decreased trabecular outflow due to choroidal congestion and higher episcleral venous pressure.[16,18] Few studies have attempted to evaluate the correlation and agreement between IOP peak and fluctuation measured during the DTC and PCT. Sakata *et al.*[5] observed a moderate correlation between IOP peaks measured with the DCT and PCT ($r = 0.419$, $P = 0.001$), but no analysis of agreement was performed. Our study indicated a strong correlation between these measurements ($r = 0.722$), but poor agreement, evidenced by a mean difference of 4.61 mmHg between IOP peaks, a wide range of the 95% limit of agreement (11.8 mmHg), and 83% of the eyes showing IOP peak differences greater than 2 mmHg. Regarding IOP fluctuation, all tests showed poor correlation and agreement, which is probably due to the fact that baseline IOP measurements for the WDT and PCT do not correspond to the lowest IOP value of the DCT.

The WDT has clinical value as a stress test to evaluate the trabecular outflow facility. Previous studies have suggested that the WDT could be used in clinical practice to estimate 24-hour IOP behavior.[5,8-10,12-15] Some have compared the mean IOP peaks obtained during the DTC and WDT.[14] However, comparing means gives no information regarding individual values, which are essential to determine if there was agreement between the measurements. Other studies have shown strong correlations between the WDT and IOP peaks obtained with a modified DTC, which included IOP measurements during office hours.[10,13,15] Vasconcelos-Moraes *et al.* found a strong correlation between the modified DCT and WDT IOP peaks ($r = 0.780$, $P < 0.0001$), but only 41% of these patients had IOP peak differences within 2 mmHg, which represents the repeatability coefficient for GAT.[22] The Bland-Altman test confirmed a poor agreement, disclosing a wide 95% CI range (12.1 mmHg). However, it is well known that IOP measurements during office hours underestimate the IOP peak over 24 hours.[11,23]

Finally, some authors have established strong correlations between the IOP peak obtained in the 24-hour DTC and the WDT,[6] but none aimed at investigating the

agreement between the measurements. Sakata *et al.* performed a WDT and 24-hour DTC in 33 normal tension glaucoma patients, and found a moderate correlation (r = 0.422) between the IOP peaks detected by both methods. Although the authors failed to perform a Bland-Altman analysis, they observed that 67% of the cases had IOP peak discrepancies that exceeded 2 mmHg, and suggested that "this rather disappointing ratio discourages estimating peak 24-hour DTC IOP by asking NTG patients to undergo a WDT".[5]

In our study, we observed a moderate correlation (r = 0.49) between the IOP peaks obtained with the DTC and WDT. Although the mean DTC IOP peak was not significantly different from that measured by the WDT (P = 0.79), the Bland-Altman plot demonstrated wide limits of agreement (17.8 mmHg). Furthermore, peak IOP differences were larger than the clinically acceptable limit of 2 mmHg in 56% of the cases, confirming the findings described by Sakata *et al.*[5] Another important feature of any test that intends to estimate peak IOP is its reproducibility. In a previous study, Medina *et al.* have demonstrated that the WTD performed at different times of the day shows poor reproducibility, which further limits its clinical use.[24]

This study presents a few limitations. The sample size was relatively small, which can limit the generalization of some of our results. Although IOP measurements at night were made with the Perkins tonometer and daytime measurements were obtained with GAT, previous studies have demonstrated excellent agreement between their readings.[25] Finally, hospitalization may artificially modify IOP behavior in individuals. However, there is no objective method that allows measurement of IOP during the night without awakening patients. Furthermore, a newly developed 24-hour telemetric contact lens with an embedded sensor that allows undisturbed estimation of IOP in POAG patients at home corroborates the existing evidence regarding the circadian IOP pattern found in previous DTC studies.[26]

To our knowledge, our study is the first to analyze not only the correlation, but also the agreement between a 24-hour DTC, the WDT and the PCT IOP peaks and fluctuations. Our findings suggest that while the DTC remains the gold standard method to assess IOP behavior, alternative tests such as the WDT and PCT, although more practical, should be used with caution to estimate peak IOP.

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Fauze Goncalves: Study conception and design; data acquisition and interpretation; article draft; final approval of the version to be published

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