Evaluation of Choroidal Thickness, Intraocular Pressure, and Serum Osmolality After the Water Drinking Test in Eyes With Primary Angle Closure

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Purpose. We evaluated changes in choroidal thickness (ChT), IOP, ocular biometry, and serum osmolality after the water drinking test (WDT) in subjects with previous acute primary angle closure (APAC) and primary angle closure glaucoma (PACG).

Methods. We evaluated 38 subjects, including 21 with APAC and 17 with PACG. Each subject underwent IOP measurement, A-scan biometry, spectral domain-optical coherence tomography (SDOCT), anterior segment-optical coherence tomography (ASOCT), and osmolality measurements at baseline, 30, and 60 minutes after consuming at least 10 mL/kg of water. The ChT at the macula was measured from SDOCT images using the 7-line scan protocol. The fellow-eyes of APAC (FE-APAC) were compared to eyes with PACG.

Results. The mean age ± SD of the study subjects was 62.8 ± 8.6 years and 21 (55.3%) were females. At baseline, serum osmolality was significantly lower ($P < 0.001$) in the FE-APAC group, whereas ChT was similar in both groups ($P = 0.56$). At 30 minutes after WDT, both groups demonstrated a significant increase in IOP (FE-APAC, 3.0 [95% confidence interval {CI}, 1.52, 4.48] mm Hg; PACG, 5.06 [95% CI, 3.68, 6.26] mm Hg; $P < 0.001$ for both) and decrease in serum osmolality ($P < 0.001$ for both), but no significant change in ChT. The magnitude of change in IOP was significantly greater in PACG eyes ($P = 0.04$). After multivariate analysis, a lower mean baseline serum osmolality ($\beta = -0.44$, $P = 0.003$) was associated with a greater change in ChT at 30 minutes after WDT.

Conclusions. The increase in IOP after WDT was higher in PACG eyes compared to FE-APAC; however, the latter had lower serum osmolality at baseline. Change in mean ChT following WDT was associated with a lower baseline serum osmolality.

Keywords: glaucoma, water drinking test, choroidal thickness, intraocular pressure, osmolality

Acute primary angle closure (APAC) is an ophthalmic emergency that can lead to poor long-term visual outcomes, such as glaucomatous optic nerve damage and blindness in the affected eye.[1,2] The fellow eyes of patients presenting with APAC are at high risk of APAC because both eyes share similar anatomical features.[3] Certain drugs, environmental factors, and systemic conditions are known to precipitate APAC,[4] but the underlying mechanisms are only partially understood, and it is not known if there is a final common pathway involved in its pathogenesis.

The water drinking test (WDT) is a provocative test that indirectly evaluates the outflow system of the eye.[5,6] An increase in IOP of 8 mm Hg after WDT is considered as indicative of risk for primary open angle glaucoma (POAG). Although, the test was used widely previously to diagnose POAG, it was later found to be wanting due to lack of standardization, and many false-positive and false-negative results.[7,8] Recently, the WDT has attracted renewed attention when it was found to be an accessible marker of osmotically induced changes in choroidal thickness (ChT).[9,10] Used as a stress test, it yields a good estimate of the peak diurnal IOP.[5] Arora et al.[10] studied changes in ChT after WDT across angle-closure and open-angle subjects. While a significant increase in ChT was noted in angle-closure eyes, the increases in IOP after the WDT were not fully explained by ChT increase alone, suggesting that there are other underlying mechanisms behind the IOP rise.[10]

Clinical studies have suggested that choroidal expansion is a possible mechanism in APAC, being found in a proportion of such patients.[11] Furthermore, within the angle closure disease spectrum, the subfoveal choroid has been shown to be thicker in APAC eyes compared to primary angle closure suspects (PACS) in cross-sectional studies.[12,13] The thicker subfoveal choroid may be a surrogate for choroidal expansion that occurs in some individuals with APAC.

Therefore, in this study, by comparing fellow eyes of APAC (FE-APAC) and primary angle closure glaucoma (PACG) eyes, we aimed to evaluate the association of changes in IOP, ChT,

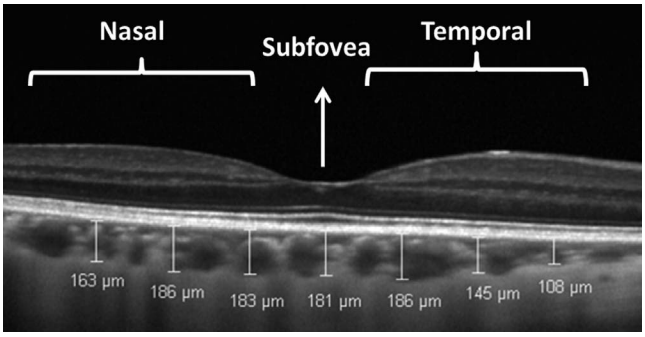

FIGURE 1. SDOCT (enhanced depth imaging) image showing measurement of macular ChT at the subfovea, and 0.5, 1, and 1.5 mm nasal and temporal to the fovea, respectively.

serum osmolality, and anterior segment structures after the WDT. We hypothesized that associations between the above factors may partly explain the predisposition for an APAC attack.

METHODS

Subjects

This prospective study was approved by the Institutional Review Board of the hospital and adhered to the provisions of the Declaration of Helsinki for research involving human subjects. Written informed consent was obtained from all participants involved in the study. One eye of each subject was included.

The two subgroups of angle closure subjects recruited into the study were FE-APAC and chronic PACG. The APAC was defined according to the following criteria.[14] Presence of at least two of the following symptoms: ocular or periocular pain, nausea and/or vomiting, and an antecedent history of intermittent blurring of vision with halos; presenting IOP of at least 22 mm Hg (as measured by Goldmann applanation tonometry), and the presence of at least three of the following signs: conjunctival injection, corneal epithelial edema, mid-dilated unreactive pupil, and a shallow anterior chamber in addition to the presence of occludable angles defined as the inability to visualize the posterior trabecular meshwork for at least 180° on nonindentation gonioscopy.[14] We diagnosed PACG on the basis of occludable angles with glaucomatous optic neuropathy (defined as vertical cup-to-disc [CDR] ratio of >0.7, CDR asymmetry >0.2, and/or focal notching) with compatible visual field loss on static automated perimetry (SITA Standard algorithm with a 24-2 test pattern; Humphrey Visual Field Analyser II; Carl Zeis Meditec, Dublin, CA, USA). This was defined as Glaucoma Hemifield Test outside normal limits; a cluster or 3 or more, nonedge, contiguous points on the pattern deviation plot, not crossing the horizontal meridian with a probability of <5% being present in age-matched normals (one of which was <1%); and an abnormal pattern standard deviation (PSD) with $P < 5\%$ occurring in the normal population, and fulfilling the test reliability criteria (fixation losses <20%, false-positives <33% and/or false-negatives <33%). All FE-APAC eyes had IOP $\leq$ 21 mm Hg and appositional angle closure on gonioscopy and no evidence of peripheral anterior synechiae (PAS) or glaucomatous optic neuropathy.

As an additional analysis, we also compared the angle closure eyes, including FE-APAC and PACG versus normal eyes. Normal subjects were defined as having an IOP < 21 mm Hg, open angles on gonioscopy, healthy optic nerves, and no family history of glaucoma. All study eyes had not had any intraocular surgery or trauma.

All subjects with angle closure had undergone laser peripheral iridotomy (LPI). The interval between LPI and the study recruitment is 37.2 ± 27.8 months (range, 7–123 months; median, 30 months). Subjects with secondary causes of angle closure, such as a phacomorphic component/subluxed lens, angle closure patients who had laser peripheral iridoplasty, corneal disorders that preclude adequate imaging of the angles, such as extensive pterygium and peripheral corneal opacity, were excluded. Subjects with a pre-existing cardiac disease, including congestive cardiac failure also were excluded.

Examination

Study subjects underwent a standardized ophthalmic evaluation, including slit-lamp biomicroscopy, IOP measurement (applanation tonometry), gonioscopy, A-scan biometry (US-800; Nidek Co. Ltd., Tokyo, Japan), spectral domain-optical coherence tomography (SDOCT, Spectralis; Heidelberg Engineering, Heidelberg, Germany), anterior segment-optical coherence tomography (ASOCT, Visante; Carl Zeiss Meditec), and venous blood serum osmolality measurements at baseline, 30, and 60 minutes after consumption of at least 10 mL/kg of water within 5 minutes.[15] Serum osmolality could not be analyzed for three subjects at baseline, and five subjects each at 30 and 60 minutes either due to poor vein access, insufficient or hemolysed specimens. Axial length (AL), anterior chamber depth (ACD), and lens thickness (LT) measurements were obtained from the A-scan biometry. Both SD-OCT and AS-OCT imaging were performed by a single masked operator.

Anterior Segment Imaging and Analysis. All subjects underwent imaging with ASOCT (Visante; Carl Zeiss Meditec) performed under standardized dark room conditions (0 lux). One cross-sectional horizontal ASOCT scan of the nasal and temporal angle was evaluated for each subject. The images were processed using customized software, the Zhongshan Angle Assessment Program (ZAAP, Guangzhou, China).[16] The parameters measured by the software include angle opening distance at 750 μm from scleral spur (AOD750); trabecular-iris space area (TISA750)[17]; anterior chamber width, area, and volume (ACW, ACA, ACV)[18,19]; lens vault[20]; iris thickness; and iris cross-sectional area.[21]

Imaging and Measurement of ChT. The choroid images were obtained by using SD-OCT (Spectralis; Heidelberg Engineering). The macular region around the fovea of the study eye was scanned using a 7-line scan protocol (scan width 30° and 25 averaging) with enhanced depth imaging (EDI). One scan at each time point was taken for each subject; however, if the image had poor visualization of the choroidal–scleral interface (CSI), the border between the choroid and sclera, an additional scan was taken. The optical magnification was estimated by entering the keratometry and refractive readings to the SD-OCT software before scanning. A single masked grader (VF) manually selected the image centered on the fovea from seven images and manually measured the ChT by using the line caliber tool, native to Heidelberg Eye Explorer software (version 5.6.1.0). The ChT was defined as the perpendicular distance from the external portion of the RPE, Bruch's membrane, to the CSI. The ChT of the fovea was measured at the thinnest/central point of the fovea. Measurements also were taken at six additional points at 0.5, 1.0, and 1.5 mm nasal and temporal to the fovea, respectively (Fig. 1). The mean ChT was calculated as the average of the seven measurements. The images from 7, 9, and 12 subjects at baseline, 30, and 60 minutes, respectively, were excluded as the CSI was not clearly visible.

Table 1. Baseline Characteristics of Study Subjects

	FE-APAC, $N = 21$	PACG, $N = 17$	*P* Value*	Normals, $N = 20$	*P* Value†
Age, y, mean (95% CI)	62.9 (59.7, 66.1)	62.6 (57.2, 68.0)	0.91	58.9 (54.3, 63.4)	0.31
Sex, male *N* (%)	06 (28.6)	11 (64.7)	**0.03**	9 (45.0)	0.98
Weight, kg, mean (95% CI)	58.6 (53.2, 64.1)	67.4 (58.6, 76.2)	0.07	73.5 (65.9, 81.1)	0.01**
IOP, mm Hg mean (95% CI)	13.1 (11.9, 14.4)	14.1 (12.3, 15.8)	0.37	13.5 (12.0, 15.0)	0.67
Osmolality mmol/kg, mean (95% CI)§	285.5 (280.6, 290.3)	295.7 (293.4, 297.9)	0.001	293.6 (291.1, 296.2)	<0.001††
ChT , μm, mean (95% CI)‖	272.0 (239.1, 304.9)	265.3 (212.2, 318.4)	0.81	213.1 (182.7, 243.5)	0.04
ChT fovea, μm, mean (95% CI)‖	275.6 (235.7, 315.6)	282.4 (225.3, 339.5)	0.83	222.8 (187.1, 258.6)	0.09
Cup-disc-ratio, mean (95% CI)	0.41 (0.36, 0.47)	0.75 (0.69, 0.81)	0.001	0.44 (0.38, 0.50)	<0.001‡‡
ACD, mm, mean (95% CI)	2.49 (2.38, 2.61)	2.79 (2.52, 3.07)	0.04	3.15 (2.97, 3.33)	<0.001§§
Axial length, mm, mean (95% CI)	22.43 (22.00, 22.85)	23.45 (22.62, 24.28)	0.02	24.03 (23.63, 24.43)	<0.001§§
LT, mm, mean (95% CI)	4.75 (4.53, 4.98)	4.72 (4.51, 4.94)	0.85	4.30 (4.07, 4.53)	0.005‖‖
Total water ml, mean (95% CI)	808.9 (704.9, 912.9)	812.2 (717.4, 907.1)	0.91‡	795.0 (704.7, 885.3)	0.96
ASOCT parameters¶					
ACW, mm, mean (95% CI)	11.24 (11.01, 11.46)	11.39 (11.11, 11.67)	0.38	11.64 (11.48, 11.81)	0.03
ACA mm^2, mean (95% CI)	13.91 (12.99, 14.83)	16.17 (14.35, 18.00)	0.03	22.24 (20.58, 23.91)	<0.001¶¶
ACV, mm^3, mean (95% CI)	87.38 (80.20, 94.56)	105.4 (90.87)	0.03	150.5 (136.4, 164.7)	<0.001¶¶
Lens vault mm, mean (95% CI)	1.00 (0.88, 1.12)	0.81 (0.63, 0.99)	0.07	0.30 (0.15, 0.45)	<0.001¶¶
Iris thickness, mm, mean (95% CI)	0.48 (0.44, 0.53)	0.49 (0.45, 0.53)	0.74‡	0.44 (0.39, 0.48)	0.12
Iris area, mm^2, mean (95% CI)	1.65 (1.55, 1.75)	1.60 (1.54, 1.68)	0.50	1.49 (1.35, 1.64)	0.11
AOD750, mm, mean (95% CI)	0.19 (0.16, 0.23)	0.24 (0.19, 0.29)	0.09	0.49 (0.39, 0.58)	<0.001¶¶
TISA750, mm, mean (95% CI)	0.11 (0.09, 0.13)	0.12 (0.09, 0.15)	0.56‡	0.25 (0.21, 0.30)	<0.001¶¶

Bonferroni's multiple comparisons, $P < 0.006$ was considered significant for ASOCT parameters (ACW, ACA, ACV, LV, iris thickness, iris area, AOD750, and TISA750). Bonferroni's multiple comparisons, $P < 0.016$ was considered significant for biometric parameters (ACD, LT, and AL). Bonferroni's multiple comparisons, $P < 0.025$ was considered significant for ChT (mean ChT and foveal ChT).

* Independent *t*-test.
† ANOVA.
‡ Mann–Whitney *U* test.
§ $N = 15$ for PACG, $N = 19$ for normal.
‖ $N = 19$ for FE-APAC, $N = 14$ for PACG, $N = 18$ for normal.
¶ $N = 19$ for FE-APAC, $N = 15$ for PACG, $N = 17$ for normal.
** FE-APAC versus normals = 0.008.
†† FE-APAC versus normals = 0.004.
‡‡ PACG versus normals < 0.001.
§§ FE-APAC versus normals < 0.001.
‖‖ FE-APAC versus normals = 0.01.
¶¶ FE-APAC versus normals < 0.001, PACG versus normals < 0.001.

Statistical Analysis

Statistical analysis was performed using the statistical package IBM SPSS Statistics for Windows (Version 21.0; IBM Corp., Armonk, NY, USA). The time points for the study were baseline, 30, and 60 minutes after the WDT. Paired *t*-test for parametric data and Wilcoxon signed-rank test for nonparametric data were used to assess the mean changes in the continuous variables from baseline at each individual time point. An appropriate Bonferroni correction ($\alpha/3$) was applied to correct for the number of time-point evaluated resulting in a *P* value threshold of 0.017 to be considered statistically significant. The between-group differences (FE-APAC versus PACG, PACG versus normals, and FE-APAC versus normals) were evaluated by independent *t*-test and Mann-Whitney *U* test for parametric and nonparametric data, respectively. Univariate linear regression analysis adjusted for age and sex were performed for baseline parameters with change in mean ChT at 30 minutes (calculated as mean ChT at 30 minutes-baseline mean ChT) as the dependent variable. This was followed by a multivariate linear regression analysis using baseline parameters that showed significance at 0.20 levels in univariate analysis, excluding those that showed multicollinearity. Variance inflation factor and tolerance were calculated to test potential multicollinearity among the independent variables. The R^2 was evaluated to examine the adequacy of the multiple linear regression models. A general linear model (GLM) for repeated measures analysis of ChT at the three time-points also was performed adjusting for covariates age, sex, baseline IOP, baseline osmolality and comparing between FE-APAC and PACG. By assuming a mean difference in ChT of 0.2 mm and a SD of 0.19 mm after WDT,[9] with power of 90% and α of 5%, the sample size for a 2-sided test was 20 subjects each for cases and controls.

Results

Demographic and Baseline Characteristics of Subjects

We recruited 21 FE-APAC and 17 PACG eyes, with only one eye per subject included. The mean age (SD) of the subjects was 61.4 (9.2) years and there were 32 (55.2%) females. Baseline characteristics of the subjects are summarized in Table 1. Compared to PACG, the FE-APAC subjects had significantly smaller CDR ($P < 0.001$). There were no significant differences in age, ACD, AL, LT, and other ASOCT parameters. Serum osmolality was significantly lower in the FE-APAC subjects compared to PACG ($P < 0.001$) at baseline. Baseline ChT was not significantly different between the two groups ($P = 0.56$).

A total of 20 normal eyes from 20 subjects each also was recruited. In the comparison of baseline characteristics between eyes with FE-APAC, PACG, and normal (Table 1), eyes

Table 2. Comparison of Changes in Parameters of Angle Closure Subjects at 30 and 60 Minutes After the WDT

	30 Minutes After WDT					60 Minutes After WDT				
	FE-APAC, $N = 21$		PACG, $N = 17$			FE-APAC, $N = 21$		PACG, $N = 17$		
	Overall Change Mean (95% CI)	*P* Value	Overall Change Mean (95% CI)	*P* Value	*P* Value	Overall Change Mean (95% CI)	*P* Value	Overall Change Mean (95% CI)	*P* Value	*P* Value
IOP, mm Hg	3 (1.52, 4.48)	0.002	5.06 (3.86, 6.26)	<0.001	0.02	0.86 (−0.68, 2.39)	0.42	2.29 (0.90, 3.69)	0.006	0.17
% IOP	25.3 (13.3, 37.3)		39.8 (28.3, 51.3)		0.04	7.1 (−4.1, 18.3)		20.0 (7.9, 32.0)		0.09
Osmolality, mmol/Kg*	−4.38 (−1.67, −7.09)	0.005	−8.29 (−10.17, −6.39)	0.001	0.02	−6.4 (−9.1, −3.7)	0.001	−8.4 (−10.9, −5.9)	0.001	0.66
% Osmolality	−1.51 (−2.45, −0.56)		−2.61 (−3.43, −2.16)		0.04	−2.1 (−3.2, −1.3)		−2.8 (−3.7, −2.0)		0.76
Mean ChT, µm†	4.31 (−5.35, 13.97)	0.65	−9.1 (−19.5, 1.3)	0.04	0.06	1.64 (−18.2, 21.5)	0.91	-9.6 (−27.5, 8.2)	0.27	0.39
% mean ChT	2.7 (−2.78, 8.41)		−3.4 (−7.37, 0.03)		0.04	1.4 (−6.9, 11.2)		−3.2 (−9.1, 2.7)		0.34
Fovea ChT, um†	12.3 (−4.1, 28.6)	0.09	−21.5 (−50.9, 7.9)	0.16	0.05	−3.4 (−42.4, 35.6)	0.72	−4.0 (−29.9, 21.9)	0.81	0.76
% ChT fovea	8.1 (−0.66, 16.8)		−7.8 (−18.5, 2.8)		0.04	8.7 (−18.0, 35.3)		1.52 (−10.1, 13.4)		0.91
ACD, mm	−0.01 (−0.11, 0.09)	0.73	−0.03 (−0.15, 0.09)	0.59	0.84	0.08 (−0.07, 0.23)	0.32	−0.14 (−0.37, 0.09)	0.25	0.18
Axial length, mm	−0.02 (−0.15, 0.11)	0.74	0.05 (−0.09, 0.19)	0.59	0.49	0.04 (−0.06, 0.14)	0.36	0.07 (−0.06, 0.19)	0.51	0.79
LT, mm	0.03 (−0.03, 0.09)	0.30	0.09 (0.02, 0.18)	0.03	0.27	−0.03 (−0.19, 0.14)	0.23	0.05 (−0.08, 0.18)	0.81	0.82
ASOCT parameters‡										
ACW, mm	−0.13 (−0.24, −0.02)	0.03	−0.01 (−0.12, 0.09)	0.75	0.18	0.05 (−0.04, 014)	0.38	0.10 (−0.01, 0.21)	0.23	0.65
ACA, mm^2	−0.14 (−0.33, 0.05)	0.11	−0.06 (−0.28, 0.16)	0.35	0.70	−0.16 (−0.45, 0.13)	0.07	−0.01 (−0.23, 0.23)	0.94	0.12
ACV, mm^3	−1.11 (−3.38, 1.15)	0.21	−0.12 (−2.63, 2.39)	0.63	0.44	−0.93 (−4.2, 2.3)	0.04	0.57 (−2.2, 3.2)	0.81	0.21
Lens vault, mm	−0.03 (−0.07, 0.02)	0.16	−0.04 (−0.07, 0.00)	0.08	0.84	0.02 (−0.04, 0.08)	0.57	0.03 (−0.04, 0.10)	0.24	0.69
Iris thickness, mm	0.004 (−0.02, 0.04)	0.79§	0.006 (−0.02, 0.04)	0.69§	0.94‖	0.001 (−0.04, 0.04)	0.93§	0.006 (−0.04, 0.05)	0.76§	0.86‖
Iris area, mm^2	0.02 (−0.06, 0.02)	0.38	−0.003 (−0.06, 0.05)	0.90	0.51	0.004 (−0.06, 0.07)	0.89	0.06 (0.01, 0.11)	0.03	0.16
AOD750, µm	0.02 (−0.01, 0.05)	0.28	0.001 (−0.02, 0.02)	0.97	0.31	−0.03 (−0.06, 0.01)	0.14	−0.04 (−0.06, −0.01)	0.02	0.85
TISA750, µm	0.005 (−0.004, 0.01)	0.29§	0.008 (−0.002, 0.02)	0.11§	0.59‖	−0.01 (−0.02, 0.01)	0.19§	−0.01 (−0.03, 0.004)	0.15§	0.87‖

* $N = 20$ for FE-APAC at 60 minutes, $N = 14$ and 15 for PACG at 30 and 60 minutes, respectively.
† $N = 18$ and 16 for FE-APAC at 30 and 60 minutes, respectively; $N = 13$ and 12 for PACG at 30 and 60 minutes, respectively.
‡ $N = 19$ and 15 for FE-APAC at 30 and 60 minutes, respectively; $N = 14$ and 11 for PACG at 30 and 60 minutes, respectively.
§ Wilcoxon signed rank test.
‖ Mann–Whitney *U* test.

TABLE 3. Comparison of Changes in Parameters Between Angle Closure Subtypes and Normals at 30 and 60 Minutes After the WDT

	30 Min After WDT				60 Min After WDT			
	Overall Change Mean (95% CI)	*P* Value	Overall Change Mean (95% CI)	*P* Value	Overall Change Mean (95% CI)	*P* Value	Overall Change Mean (95% CI)	*P* Value
	PACG, $N = 17$		**Normals, $N = 20$**		**PACG, $N = 17$**		**Normals, $N = 20$**	
IOP, mm Hg	5.06 (3.86, 6.26)	<0.001	3.05 (2.09, 4.00)	<0.001	2.29 (0.90, 3.69)	0.006	0.40 (−0.33, 1.13)	0.26
% IOP	39.8 (28.3, 51.3)		24.8 (16.2, 33.2)		20.0 (7.9, 32.0)		2.8 (−2.8, 8.4)	
Osmolality mmol/kg*	−8.29 (−10.17, −6.39)	<0.001	−5.06 (−6.68, −3.42)	<0.001	−8.4 (−10.9, −5.9)	0.001	−6.5 (−8.7, −4.2)	<0.001
% Osmolality	−2.61 (−3.43, −2.16)		−1.72 (−2.26, −1.17)		−2.8 (−3.7, −2.0)		−2.1 (−2.9, −1.4)	
Mean ChT, μm†	−9.1 (−19.5, 1.3)	0.04	−0.55 (−9.3, 8.2)	0.85	−9.6 (−27.5, 8.2)	0.27	0.50 (−8.4, 9.4)	0.82
% mean ChT	−3.4 (−7.37, 0.03)		0.05 (−4.10, 4.21)		−3.2 (−9.1, 2.7)		0.16 (−3.8, 4.2)	
	FE-APAC, $N = 21$		**Normals, $N = 20$**		**FE-APAC, $N = 21$**		**Normals, $N = 20$**	
IOP, mm Hg	3 (1.52, 4.48)	0.002	3.05 (2.09, 4.00)	<0.001	0.86 (−0.68, 2.39)	0.41	0.40 (−0.33, 1.13)	0.26
% IOP	25.3 (13.3, 37.3)		24.8 (16.2, 33.2)		7.1 (−4.1, 18.3)		2.8 (−2.8, 8.4)	
Osmolality mmol/kg*	−4.38 (−1.67, −7.09)	0.005	−5.06 (−6.68, −3.42)	<0.001	−6.4 (−9.1, −3.7)	0.001	−6.5 (−8.7, −4.2)	<0.001
% Osmolality	−1.51 (−2.45, −0.56)		−1.72 (−2.26, −1.17)		−2.1 (−3.2, −1.3)		−2.1 (−2.9, −1.4)	
Mean CT, μm†	4.31 (−5.35, 13.97)	0.65	−0.55 (−9.3, 8.2)	0.85	1.64 (−18.2, 21.5)	0.79	0.50 (−8.4, 9.4)	0.83
% mean CT	2.7 (−2.78, 8.41)		0.05 (−4.10, 4.21)		1.4 (−6.9, 11.2)		0.16 (−3.8, 4.2)	

* $N = 20$ for FE-APAC at 60 minutes; $N = 14$ and 15 for PACG at 30 and 60 minutes, respectively; $N = 18$ for normal at 30 and 60 minutes.
† $N = 18$ and 16 for FE-APAC at 30 and 60 minutes, respectively; $N = 13$ and 12 for PACG at 30 and 60 minutes, respectively; $N = 18$ for normal at 30 and 60 minutes.

with either FE-APAC or PACG had significantly smaller ACA and ACV, narrower anterior chamber angles, and larger lens vault (LV, $P < 0.006$ for all). The lens was thicker in FE-APAC compared to normals ($P = 0.01$). The FE-APAC subjects also were noted to have significantly lower serum osmolality at baseline compared to normal ($P = 0.004$). Overall, majority of our subjects were of Chinese ethnicity ($N = 49$, 84.5%).

Post-WDT Comparison Between FE-APAC and PACG Eyes

At 30 minutes after the WDT, as summarized in Table 2, there was a significant increase in IOP and decrease in serum osmolality in both groups (pairwise $P < 0.017$ for all), while a significant increase in IOP at 60 minutes was noted only in the PACG group ($P < 0.006$). The PACG eyes experienced a significantly higher increase in IOP (FE-APAC 3.0 [95% confidence interval {CI}, 1.52, 4.48 mm Hg versus PACG 5.06 [95% CI, 3.68, 6.26 mm Hg; $P = 0.02$]) and greater decrease in serum osmolality compared to FE-APAC subjects ($P = 0.02$).

An increase in mean ChT was noted in FE-APAC compared to PACG eyes at 30 minutes (4.3 [95% CI, −5.35, 13.97] μm versus −9.1 [95% CI, −19.5, 1.3] μm), but the difference was not statistically significant ($P = 0.06$). No significant differences in the changes in biometric and ASOCT parameters were noted either within (pairwise $P > 0.017$ for all) or between ($P > 0.05$) the two groups at 30 and 60 minutes. The GLM with repeated measures analysis comparing FE-APAC and PACG for change in ChT, showed borderline significance of $P = 0.052$ for baseline osmolality at an observed power of 58%.

Post-WDT Comparison Between Angle Closure Groups and Normal Eyes

At 30 minutes after the WDT, as summarized in Table 3, there was a significant increase in IOP and decrease in serum osmolality within all the groups (pairwise $P < 0.017$ for all), while a significant increase in IOP at 60 minutes was noted only in the PACG group ($P < 0.006$). Compared to normal eyes, only the PACG eyes experienced a significantly higher increase in IOP ($P = 0.01$) and a greater decrease in serum osmolality compared to normal eyes ($P = 0.01$). No significant differences in ChT were noted either within (pairwise $P > 0.017$ for all) or between ($P > 0.05$) the groups at 30 and 60 minutes.

Comparison of changes in biometric and ASOCT parameters also showed no significant differences either within (pairwise $P > 0.017$ for all) or between ($P > 0.05$) the groups at 30 and 60 minutes (data not shown).

Figures 2 to 4 illustrate the inter-relation among IOP, osmolality, and ChT changes following the WDT. In the three groups, there was an initial rise in IOP and a concomitant drop in serum osmolality. In FE-APAC, the ChT increased from baseline to 30 minutes after the WDT, while in PACG eyes, the ChT initially decreased at 30 minutes followed by an increase at 60 minutes after WDT. In the normals, the ChT remained largely unchanged.

Age- and sex-adjusted univariate linear regression analysis performed for baseline predictors of change in ChT at 30 minutes showed a significant association with lower serum osmolality and a thinner lens. The multivariate linear regression model found significant associations with lower baseline serum osmolality ($P = 0.005$, $R^2 = 0.26$, Table 4). No significant predictors were associated with change in IOP at 30 minutes after WDT.

At 60 minutes, the IOP of 4 subjects were noted to be >21 mm Hg; two with IOP of 22 mm Hg, one with 23 mm Hg, and another 24 mm Hg. The IOP were rechecked after half an hour

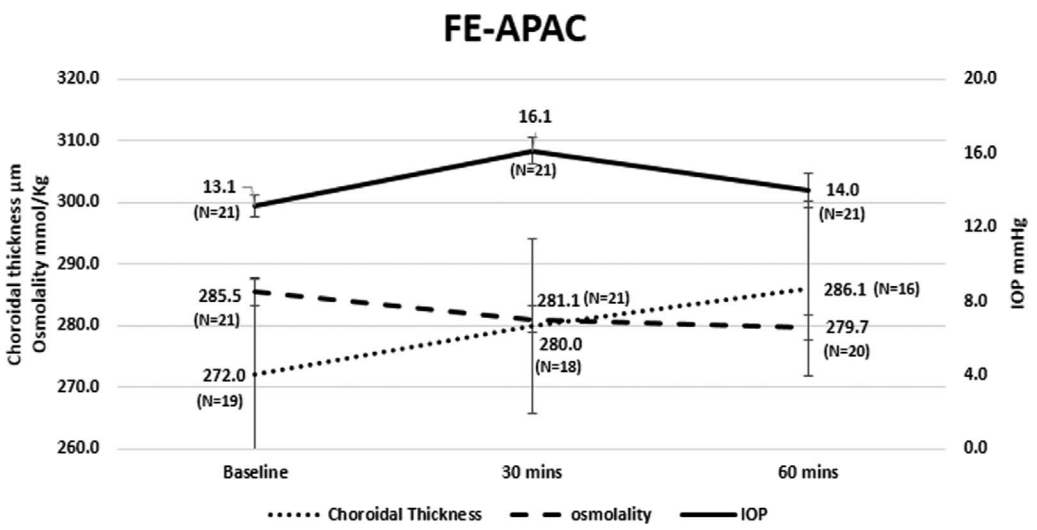

Figure 2. Illustration of the change in IOP, osmolality, and ChT at 30 and 60 minutes following the WDT in FE-APAC subjects.

and were noted to have spontaneously reduced to <21 mm Hg for all four subjects without any intervention. The intra-observer reproducibility of ChT measurements assessed in a random subset of 10 eyes was excellent at 0.92 (95% CI, 0.62–0.98) for mean ChT and 0.93 (95% CI, 0.71–0.98) for subfoveal ChT.

Discussion

In this study, we investigated the concurrent effects of the WDT on serum osmolality, ChT, anterior segment biometry, and IOP in FE-APAC and PACG eyes. The FE-APAC group had a significantly lower baseline serum osmolality compared to the PACG group. At 30-minutes after WDT, both groups showed significant IOP increases and serum osmolality decreases, but no significant changes in ChT, even though a trend was noted in FE-APAC eyes. At 60 minutes, only PACG eyes had sustained IOP elevations. Notably, the serum osmolality levels even after the WDT-induced reduction were within the normal reference range for all subjects.

While the FE-APAC group had a lower baseline osmolality, the PACG group experienced a greater drop in serum osmolality after WDT. Osmotic gradient may be a possible factor influencing IOP changes in some patients as the gradient leads to water movement into the aqueous humour with subsequent increase in IOP.[22] It is not known whether the lower baseline osmolality in FE-APAC eyes predisposes them to a greater risk of APAC; such an association may be difficult to establish in the current study. Of note, all FE-APAC and PACG eyes had previously undergone a prophylactic laser iridotomy before the WDT which may alter the fluid dynamics. A lower baseline serum osmolality was significantly associated with a corresponding change in mean ChT at 30 minutes after WDT. The rapid water ingestion would lead to a transient increase in hydrostatic pressure and decrease in osmotic pressure, which shifts fluid from the systemic circulation to the choroidal space due to the osmotic gradient.[22] The change in choroidal volume would be transmitted to the intraocular compartments causing fluid exit via the outflow facility by trabecular and uveoscleral pathways.[11] Eyes may show a higher or lower IOP elevation depending on its outflow facility, as suggested by Brubaker.[23] Interestingly, our findings of the lack of significant association between IOP rise and change in ChT were similar to the

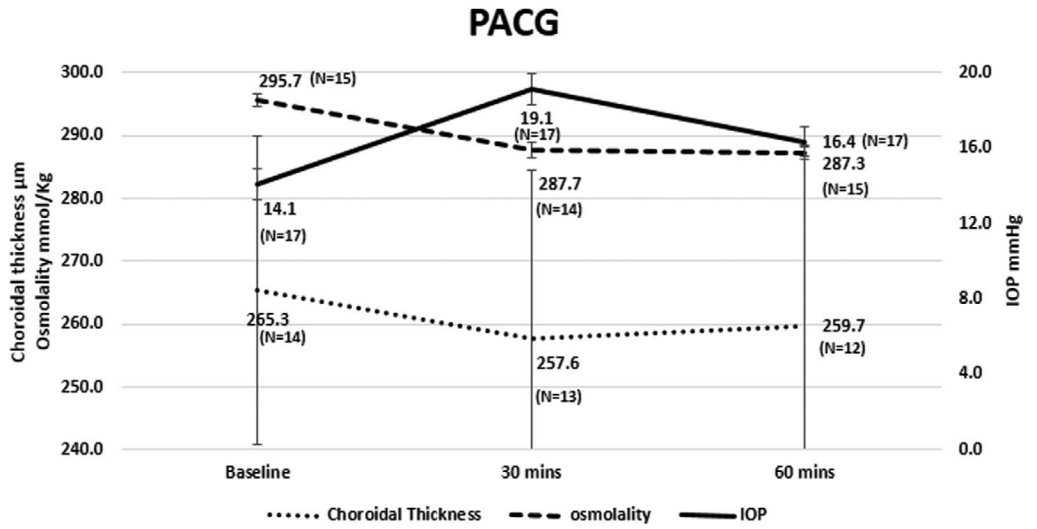

Figure 3. Illustration of the change in IOP, osmolality, and ChT at 30 and 60 minutes following the WDT in PACG subjects.

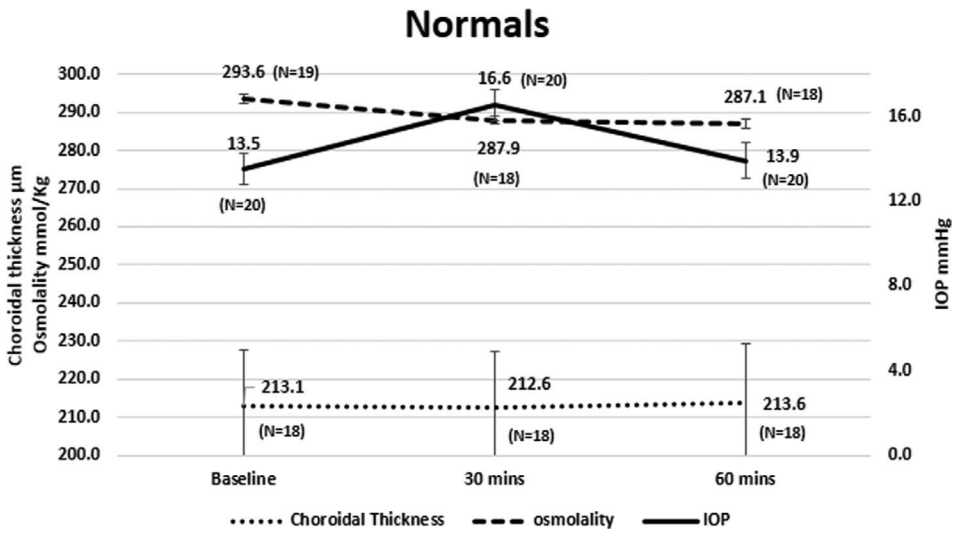

Figure 4. Illustration of the change in IOP, osmolality, and ChT at 30 and 60 minutes following the WDT in normal subjects.

findings reported by Arora et al.[10] and Mansouri et al.[24] In the study by Arora et al.[10] on the changes in ChT after WDT across angle-closure and open-angle subjects, it was proposed that the lack of significant changes in ChT during the WDT across all groups may have resulted from the concomitant increase in blood pressure (BP) and IOP, which, therefore, resulted in the perfusion pressure to remain unchanged.[10] While our study did not evaluate the changes in BP, we presumed a similar effect of the WDT on BP in our subjects. Mansouri et al.[24] speculated that choroidal expansion is an unlikely primary mechanism responsible for the IOP elevations induced by the WDT. Another possibility for the lack of association between IOP rise and ChT in our study could be due to the small sample size.

The association between serum osmolality reduction and IOP elevations has been investigated by numerous studies during and after hemodialysis in end-stage renal failure patients, only to give mixed results.[25–29] There seems to be a tendency for IOP to increase during hemodialysis in patients with narrow angles due to abnormal aqueous outflow.[26] These studies suggest that serum osmotic gradient is possibly the driving mechanism for IOP alterations in conventional hemodialysis, and support the theory of a significant inverse correlation between serum osmolality and IOP rise. The removal of solutes during hemodialysis leads to a decrease in

Table 4. Factors Associated With Change of Mean ChT From Baseline to 30 Minutes After the WDT

	Univariate			Multivariate $R^2 = 0.26$			
Variables	B (CI)	Beta	*P* Value	B (CI)	Beta	*P* Value	Tolerance
Age, y, mean	−0.05 (−0.65, 0.54)	−0.03	0.86	0.40 (−0.29, 1.09)	0.19	0.25	0.59
Sex (male/female)	4.33 (−7.31, 15.97)	0.12	0.46	−1.66 (−14.0, 10.7)	−0.04	0.79	0.64
Diagnosis (Ref: normals)							
FE-APAC	7.45 (−5.32, 20.22)	0.19	0.25				
PACG	−9.33 (−22.87, 4.22)	−0.22	0.17	−0.48 (−18.8, 17.9)	−0.01	0.96	0.37
Weight, kg, mean	0.34 (−0.11, 0.78)	0.28	0.13	0.34 (−0.10, 0.77)	0.28	0.12	0.51
IOP, mm Hg, mean	0.60 (−1.12, 2.33)	0.10	0.48				
Osmolality, mmol/kg, mean	−0.91 (−1.52, −0.30)	−0.42	0.004	−0.94 (−1.59, −0.30)	−0.44	0.005	0.76
Mean ChT, µm, mean	−0.05 (−0.11, 0.02)	−0.19	0.19	−0.05 (−0.11, 0.02)	−0.21	0.14	0.85
ChT Fovea, µm, mean	−0.02 (−0.08, 0.04)	−0.09	0.52				
Cup-disc-ratio	−21.09 (−51.6, 9.4)	−0.21	0.17	−12.01 (−54.54, 30.45)	−0.12	0.57	0.41
ACD, mm, mean	−2.22 (−15.51, 11.06)	−0.05	0.74				
Axial length, mm, mean	−2.01 (−7.02, 3.00)	−0.14	0.42				
LT, mm, mean	−11.28 (−21.94, −0.63)	−0.31	0.04	−6.91 (−17.96 4.14)	−0.19	0.21	0.77
Total water, ml	0.02 (−0.01, 0.05)	0.18	0.28				
AOD, mm	−3.95 (−34.4, 26.5)	−0.26	0.79				
TISA, mm^2	−12.40 (−73.1, 48.3)	−0.07	0.68				
ACW, mm	−4.34 (−16.2, 7.6)	−0.74	0.47				
ACA, mm^2	−0.36 (−1.69, 0.96)	0.58	0.58				
ACV, mm^3	−0.05 (−0.22, 0.12)	−0.10	0.55				
Lens vault, mm	−2.13 (−16.6, 12.3)	−0.05	0.76				
Iris thickness, mm	44.48 (−29.5, 118.4)	0.20	0.23				
Iris area, mm^2	1.89 (−25.0, 28.8)	0.02	0.88				

plasma osmolality in the cellular compartment, followed by an influx of fluid into the ciliary body, which induces an increase in the production of aqueous humor, thereby resulting in elevated IOP.[30] Furthermore, the rate of the serum osmolality decrease also could have an effect on IOP rise. In an animal study (on mongrel dogs), Sitprija et al.[25] showed that a rate of decline of 11 mOsm/kg H_2O/h in plasma osmolality was associated with a significant increase in IOP; however, with a slower rate of decline in plasma osmolality (8.5 mOsm/kg H_2O/h), the rise increase in IOP was minimal. This may explain the absence of significant effect of WDT on ChT in our study and the differences seen in ChT between normal and angle closure eyes in the study by Arora et al.[11] Whether lowered serum osmolality or its rate of alterations in susceptible eyes predisposes them to an acute attack is difficult to ascertain. Further exploratory studies are necessary to demonstrate such an association.

The higher IOP elevations in PACG eyes compared to the FE-APAC after the WDT could be attributed to a greater impairment of aqueous outflow in PACG eyes; since FE-APAC eyes were characterized by the absence of signs of trabecular damage, such as PAS and/or elevated IOP, iris whorling, "glaucomfleken" lens opacities, or excessive pigment deposition on the trabecular surface.[31] The outflow facility in the FE-APAC eyes is more capable of adapting to aqueous output alterations. Furthermore, chronic trabecular damage also could explain the significant sustained increase in IOP at 60 minutes in the PACG group.

While rapid choroidal expansion may contribute to the process of angle closure through forward anterior lens movement causing pupillary block,[11] IOP increase does not solely arise from the increase in ChT.[10,24] From our study, it may be postulated that the net IOP elevation could perhaps be a result of serum osmolality changes induced by the WDT coupled with trabecular damage in glaucomatous eyes leading to impaired aqueous outflow, which also may affect the choroid to some extent. Larger magnitude of alterations in the dynamic relationships between a lowered baseline osmolality, BP, greater osmotic gradient, choroidal expansion, and structurally-predisposed eyes may explain why some eyes develop an acute attack and others not.

To our knowledge, our study is the first to examine differences in responses to the WDT between FE-APAC and PACG eyes in terms of serum osmolality, IOP, and mean ChT changes which occur independently of angle width alterations. We chose to evaluate FE-APAC as it is the nearest surrogate to an eye with APAC.[3] However, we would like to emphasize that the experimental conditions in this study might not entirely simulate the rapid changes that likely occur during an acute episode including that of the angle alterations. Limitations of our study include the relatively small sample size which needs validation in a larger cohort. Additionally, the manual method for estimation of ChT and the limited area of assessment may not be firstly, reflective of, and secondly, capable of accurately quantifying the magnitude of the osmotic changes. We also did not evaluate for changes in circumpapillary ChT. Availability of automated image analysis software with an ability to estimate choroidal volume may result in a more accurate estimation of the changes that occur in the choroid. Ideally, long-term prospective studies evaluating changes in the dynamic relationships between systemic and ocular parameters in angle closure eyes may help identify inciting events for an acute attack, but such studies will be difficult to execute.

In conclusion, we found that the increase in IOP after WDT was higher in PACG eyes compared to FE-APAC; however, the latter had lower serum osmolality at baseline. Change in mean ChT following WDT was associated with a lower baseline serum osmolality.

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