Choroidal Thickness Change after Water Drinking Is Greater in Angle Closure than in Open Angle Eyes

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PURPOSE. To study change in choroidal thickness (CT) after water drinking test (WDT), comparing angle closure (AC) to open angle (OA) eyes.

METHODS. Before and 30 minutes after drinking 1 L of water, 88 glaucoma subjects underwent measurements of CT by spectral domain-optical coherence tomography, IOP, blood pressure (BP), axial length (AL), and anterior chamber depth (ACD).

RESULTS. Baseline CT was significantly greater in AC than in OA eyes ($P = 0.002$). After WDT, BP, IOP, and AL increased significantly (all $P \leq 0.0001$). Mean CT increased significantly in the AC group ($5.6 \mu\text{m}$, $P = 0.04$, $n = 40$) and among 80 subjects whose IOP rose > 2 mm Hg (responders; $3.2 \mu\text{m}$, $P = 0.048$), but not in the OA group or among all subjects ($2.5 \mu\text{m}$ increase overall, $<1\%$ of baseline CT, $P = 0.10$). ACD decreased in AC ($-18 \mu\text{m}$, $P = 0.07$), but not in OA eyes ($+3 \mu\text{m}$, $P = 0.74$). AC eyes had a significantly greater IOP increase after WDT than OA eyes ($P = 0.002$, multivariate regression). Among responders, CT increased more in those with larger diastolic perfusion pressure increase and in AC compared to OA eyes ($P = 0.04$ and $P = 0.053$, respectively, multivariate regression).

CONCLUSIONS. A significant increase in CT and a decrease in ACD after WDT were observed in AC but not in OA eyes, and IOP increased significantly more in AC than in OA eyes, suggesting that the dynamic behavior of the choroid may play a role in the AC process. IOP increase after the WDT was not fully explained by CT increase. (*Invest Ophthalmol Vis Sci.* 2012; 53:6393–6402) DOI:10.1167/iovs.12-10224

The choroid is the vascular supply for the outer retina and retinal pigment epithelium and helps to regulate ocular volume and temperature.¹ Abnormalities in choroidal structure

and function likely contribute to major ocular diseases.^{2–7} The development of methods such as partial coherence interferometry and spectral domain-optical coherence tomography (SD-OCT),^{8–10} which allow measurement of the choroid in vivo, has made possible investigations into the role of the choroid in ocular diseases. Before the development of SD-OCT, histological studies had reported the choroid to be thinner in glaucoma.^{11–13} Subsequent studies using SD-OCT found no association between glaucoma damage and choroidal thickness (CT) and have additionally shown that CT is associated with other factors, including age, axial length (AL), central corneal thickness (CCT), and perfusion pressure (PP).^{14–18}

The relation of CT to PP suggests that CT varies dynamically, as supported by studies demonstrating that CT varies diurnally and with change in body position.^{19–21} In addition, the achievement of emmetropia is now known to depend on active mechanisms that sense image blur, alter CT to move the retina to reduce the blur, and permanently alter scleral dimensions to maintain clear imagery.^{22–24} Change in CT is the mechanism for moving the retina to the correct position, as shown in laboratory investigations in chickens and mammals. Similar changes in CT in humans have recently been demonstrated in response to short-term unilateral image blur.²⁵

Hypothetically, expansion of the choroid would raise IOP in the short term, leading to increased exit of aqueous from the anterior chamber to return IOP to its equilibrium level.^{26–28} Because this would decrease anterior chamber volume, there would be a compensatory forward movement of the iris and lens.^{26–28} This could increase resistance for aqueous movement through the iris-lens channel (pupil block) and contribute to the development of angle closure (AC) in predisposed eyes.^{26–28} A given expansion of the choroid would likely have a disproportionately greater effect in altering IOP in smaller eyes, which are known to be at greater risk for AC. Therefore, we seek to develop methods that would measure dynamic changes in CT, as the individual tendency to choroidal expansion may be a predictive parameter for later development of angle closure glaucoma (ACG). Ideal predictive testing is not now available, as shown by the inability of present screening methods to identify those developing AC.²⁹ It has been suggested that more than 20 million people in the world have ACG,³⁰ and there are 10 times more persons who have risk factors for this disease (such as small eye dimensions) for each person who will ultimately develop it.²⁹ Although laser iridotomy treatment is an effective preventive therapy, we must consider the large numbers of people involved and the undesirability and cost of treating 10 eyes for each eye that receives a benefit.

For nearly 60 years, it has been known that rapidly drinking 1 L of water causes an increase in IOP within 30 minutes.^{31–36} The IOP increase in this water drinking test (WDT) is a predictive risk factor for development of open angle glaucoma (OAG),³⁷ but it has not been studied, to our knowledge, in AC patients. The WDT is used both diagnostically and therapeutically in systemic autonomic dysfunction and orthostatic

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hypertension. The mechanism by which it increases blood pressure (BP) is thought to be increased sympathetic tone.³⁸ Present evidence suggests that both higher IOP and increase in BP may result from increased peripheral vascular resistance, along with a minor reduction in plasma osmolality.^{39–42} It is now known that the thickness of the choroid is altered by changes in BP and IOP.¹⁴ If the net effect in the WDT were to be an increase in CT, as suggested in a prior report,³¹ IOP would be expected to increase. In this study, we obtained SD-OCT images of the choroid in glaucoma patients to determine if the WDT causes changes in CT, and if the choroidal response differs between OA and AC eyes.

METHODS

Subject Recruitment

Participants were selected as a convenience sample of patients at the Johns Hopkins Glaucoma Center of Excellence. One eye of each subject was included. Subjects were older than 18 years, had clear ocular media, and were diagnosed as AC suspect (ACS), AC, ACG, OAG suspect (OAGS), or OAG. Diagnoses were based on criteria by Foster et al.⁴³ and applied by one of us (H.Q.). Subjects were asked to join the study at times when a staff member was available to perform the necessary testing. Exclusion criteria included any retinal or neuro-ophthalmologic disease, intraocular surgery during the previous 6 months, a functioning trabeculectomy or tube-shunt surgery, secondary glaucoma, or consumption of any liquids in the 2 hours before testing. Only one patient with a past history of trabeculectomy, who had a flat, nonfunctioning bleb and was on maximum medical therapy for IOP lowering, was included. There were three ACS eyes that had not undergone laser peripheral iridotomy (LPI), whereas all other AC eyes had prior LPI. The study was approved by the Johns Hopkins Institutional Review Board and oral consent was obtained from all subjects. The study abided by the tenets of the Declaration of Helsinki.

Study Procedures

The examination protocol was conducted in a seated, resting position. BP and heart rate measurements were obtained using an automatic blood pressure cuff (Datascopie Corp., Paramus, NJ; median of three measurements), followed by measurement of IOP (average of two measurements) using the iCare tonometer (Icare Finland Oy, Espoo, Finland). AL (median of three measurements), anterior chamber depth (ACD; average of two measurements), and keratometry (average of two readings) were then measured using the IOL Master (Carl Zeiss Meditec, Inc., Dublin, CA), and SD-OCT scans of the macular region were obtained using the Heidelberg Spectralis (Heidelberg Instruments, Inc., Heidelberg, Germany).

Each participant was provided 1 L of bottled water at room temperature and given 15 minutes to drink the water. The participant was asked not to consume any additional food or beverages. Thirty minutes after the patient had finished drinking the water, the procedures described previously were repeated, and the CCT was measured using the Accutome PachPen (Accutome, Inc., Malvern, PA).

The SD-OCT images were obtained using enhanced depth imaging, in which the focus is more posterior than in retinal SD-OCT images. The macular region was scanned using a single 30° linear scan centered on the fovea. Several scans were obtained, and the image with the best visualization of the border between the choroid and sclera, the choroidal-scleral interface (CSI), was chosen as the reference/baseline image. The follow-up feature in the software was used to acquire the post-WDT images 30 minutes later, allowing the same macular section to be scanned as in the baseline image.

Keratometry readings and the most recent refraction were entered into the Heidelberg Explorer Software (Heidelberg Instruments, Inc.) to estimate optical magnification and, therefore, to allow for more

accurate comparisons across individuals. We have previously shown that failure to correct for these variables significantly affects thickness estimation.¹⁴

Image Analysis

Images were analyzed as described previously by Maul et al.¹⁴ One pre- and one post-WDT choroidal image were selected for each eligible eye. All selected images, as well as the scaling factor correcting for magnification, were exported from the SD-OCT. Because the images had a fixed size, but different optical magnifications, the $\mu\text{m}/\text{pixel}$ scale was different in the width dimension for each image. To analyze the images using a uniform method, the images were rescaled to a unified scale using Photoshop CS5 (Adobe Systems Incorporated, San Jose, CA). A grid centered at the fovea and extending 3 mm (with two 1.5-mm segments) on either side was overlaid on the images. The images were then de-identified, so that the image grader was masked to the identity and diagnosis of the subject, as well as to whether the images were acquired pre- or post-WDT. Finally, the images were analyzed using ImageJ software (National Institutes of Health, Bethesda, MD). The choroid was manually outlined, with the anterior border at the basal aspect of retinal pigment epithelium, which had a clear boundary in nearly every image. The posterior boundary, or CSI, was more variable among the images. In the majority of images, there was a hyperreflective line between the large vessel layer of the choroid and the sclera, which we marked as the CSI. When the image contained a CSI that seemed to be well delineated and thinner than the RPE, it was graded as “good.” If the CSI seemed to be thicker than the RPE, the image was classified as “fair,” and the CSI was marked at a position on the thick CSI zone that was one RPE thickness posterior to the anterior margin of this thick zone.¹⁴ Finally, in a few images, there was a hazy or incomplete boundary for the CSI; these images, still able to be graded, were classified as “acceptable,” and the posterior choroid was marked as a smooth line joining the parts of the CSI that were clearly visible. Once the anterior and posterior boundaries were marked, the area occupied by the choroid over a 6-mm-long segment was measured and used to calculate the average CT. Separate analyses were performed in which only the good and fair images were included (77 of the 88 eyes). None of the findings reported here were substantially different between the 77-eye subset and the overall 88-eye group (see Table 3); hence, we included all eyes regardless of image quality grade in the statistical analysis.

Data Analysis

Demographic data as well as pre- and post-WDT measurements were tabulated. One eye was excluded from analysis when assessing change in ACD after the WDT, as the change in ACD ($-93.5 \mu\text{m}$) was far outside the range of measured change in other subjects ($-31 \mu\text{m}$ to $28 \mu\text{m}$), likely due to instrument operator error. For some outcomes (e.g., BP or AL), two or three repeat measurements were available; in these, the median was used for analysis. The significance of change in a continuous variable was determined using paired *t*-test for normally distributed variables and Wilcoxon signed-rank test for non-normal variables. Findings for OA compared with AC eyes were contrasted by *t*-test for normally distributed variables; Wilcoxon rank-sum test for continuous, non-normal variables; and Fisher's exact test for categorical variables. Univariate linear regression analysis was conducted to relate each measured parameter to change in CT, to change in IOP, and to percentage change in CT and IOP. Multivariate linear models were constructed using variables that had univariate significance of 0.2 or smaller and using the stepwise selection method, with the criterion for entering into the model and staying in the model set at 0.10. A variable was considered to be statistically significant in a multivariate model if the significance level was less than or equal to 0.05. To determine what factors were associated with an increase in CT or IOP in those with an IOP increase of more than 2 mm Hg, separate univariate and multivariate analyses were conducted for these 80 of 88 eyes (referred

TABLE 1. Demographic Characteristics of Study Population

Characteristic	Overall, <i>n</i> = 88	OAGS/OAG, <i>n</i> = 48	ACS/AC/ACG, <i>n</i> = 40	<i>P</i> Value†
AL, mm, median (IQ)	23.6 (1.8)	24.1 (1.8)	22.7 (1.6)	<0.0001
ACD, mm, median (IQ)	3.14 (0.90)	3.48 (0.77)	2.77 (0.43)	<0.0001
CDR, mean (SD)	0.58 (0.22)	0.65 (0.22)	0.51 (0.21)	0.003
Baseline CT, μ m, mean (SD)	271 (118)	235 (82)	314 (139)	0.002
VF MD, dB, median (IQ)*	-1.67 (3.37)	-2.06 (3.68)	-0.80 (2.82)	0.01
SPP, mm Hg, median (IQ)	108.5 (18.2)	105.0 (16.2)	112.5 (20.8)	0.02
No. of glaucoma meds, <i>n</i> (%)				
None	45 (51)	19 (40)	26 (65)	0.02‡
1	20 (23)	14 (29)	6 (15)	
2	8 (9)	6 (12)	2 (5)	
3 or more	15 (17)	9 (19)	6 (15)	
SBP, mm Hg, mean (SD)	124.7 (15.8)	121.2 (15.3)	128.9 (15.6)	0.02
Female sex, <i>n</i> (%)	51 (58)	23 (48)	28 (70)	0.051
Prostaglandin, <i>n</i> (%)	37 (42)	24 (50)	13 (32)	0.13
Beta-blocker, <i>n</i> (%)	22 (25)	15 (31)	7 (18)	0.22
Age, y, median (IQ)	70.6 (12.6)	70.6 (11.9)	70.7 (11.8)	0.44
Ethnicity, <i>n</i> (%)				
White	61 (69)	35 (73)	26 (65)	0.49
Non-white	27 (31)	13 (27)	14 (35)	
Pseudophakic eye, <i>n</i> (%)	18 (20)	11 (23)	7 (18)	0.60

CDR, cup-to-disc ratio; IQ, interquartile range; meds, medicines; *n*, number of participants in category; SBP, systolic blood pressure; SPP, systolic perfusion pressure; VF, visual field.

* OAGS/OAG: *n* = 47; Overall: *n* = 87.

† Significance of difference between the OAGS/OAG and ACS/AC/ACG subgroups: Fisher's exact test, *t*-test, or Wilcoxon rank-sum test.

‡ Significance of difference between none and one or more glaucoma medications.

to here as responders). All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Of 88 persons (eyes) who completed the WDT, 48 had either OAG or OAGS, whereas 40 had ACS, AC, or ACG (Table 1). All but three of the ACS eyes and all AC and ACG eyes had undergone past LPI. The two major diagnostic groups (OA and

AC) did not differ significantly in age or ethnicity, but there was a larger percentage of females in the AC than in the OA group. As expected, the AC group had significantly shorter AL and ACD. Systolic PP and systolic BP were greater in AC patients, as was baseline CT. The OA group had significantly larger mean cup/disc ratio, worse average mean deviation (MD) in field testing, and a greater number of topical glaucoma medications in active use than the AC group.

After the WDT, there was no significant change in mean CT, either in all 88 patients considered together or in the OA group

FIGURE 1. Scatter plot of percent change in intraocular pressure and percent change in choroidal thickness, all participants (*n* = 88).

TABLE 2. Change in Parameters after WDT

Characteristic	Overall Change		OAGS/OAG Change		ACS/AC/ACG Change		P Value†
	n = 88	P Value‡	n = 48	P Value‡	n = 40	P Value‡	
CT, μ m, mean (SD)	2.54 (14.32)	0.10	0.03 (11.95)	0.99	5.55 (16.38)	0.04	0.08
% CT, mean (SD)	0.7 (4.6)	0.13	0.2 (4.3)	0.80	1.4 (4.8)	0.07	0.19
SBP, mm Hg, median (IQ)	9.00 (15.00)	<0.0001	8.00 (12.50)	<0.0001	12.00 (20.50)	<0.0001	0.42
DBP, mm Hg, median (IQ)	4.50 (4.00)	<0.0001	4.25 (5.00)	<0.0001	4.75 (4.50)	<0.0001	0.57
MBP, mm Hg, median (IQ)	6.50 (7.17)	<0.0001	5.67 (6.50)	<0.0001	6.67 (9.00)	<0.0001	0.50
IOP, mm Hg, median (IQ)	5.00 (5.00)	<0.0001	4.25 (3.50)	<0.0001	6.00 (5.75)	<0.0001	0.004
% IOP, median (IQ)	38.1 (30.6)	<0.0001	34.5 (30.1)	<0.0001	46.2 (37.1)	<0.0001	0.03
AL, mm, mean (SD)*	0.012 (0.023)	<0.0001	0.009 (0.025)	0.01	0.016 (0.022)	<0.0001	0.21
SPP, mm Hg, median (IQ)	2.50 (15.50)	0.01	2.75 (13.50)	0.02	2.25 (18.75)	0.23	0.67
ACD, mm, mean (SD)*	-0.007 (0.065)	0.34	0.003 (0.066)	0.74	-0.018 (0.061)	0.07	0.13
DPP, mm Hg, median (IQ)	-1.75 (7.00)	0.20	-1.50 (7.50)	0.398	-1.75 (9.50)	0.10	0.21

DBP, diastolic blood pressure; DPP, diastolic perfusion pressure; MBP, mean blood pressure.

* OAGS/OAG: $n = 47$; Overall: $n = 87$.

† Significance of difference between the OAGS/OAG and ACS/AC/ACG subgroups: Fisher's exact test, t -test, or Wilcoxon rank-sum test.

‡ Significance of change within population: paired t -test, or Wilcoxon signed-rank test.

(Table 2). The mean CT increase in all patients was approximately 2.5 μ m, or approximately 1% of normal CT. There was, however, a significant increase in CT in the AC group (5.5 μ m, $P = 0.04$). CT also increased significantly among the 80 subjects whose IOP rose more than 2 mm Hg (3.2 μ m, $P = 0.048$). Mean ACD decreased in all patients considered together, although this decrease was not significant (mean decrease = -7 μ m, $P = 0.34$). A mean decrease of -18 μ m in ACD was observed in the AC group, but this was of borderline significance ($P = 0.07$). In pseudophakic AC patients ($n = 7$), the mean decrease in ACD was even greater (-52 μ m); the significance of this finding could not be reliably assessed because of the small sample size. In the OA group, a small, statistically insignificant increase in mean ACD was observed (+3 μ m, $P = 0.74$); pseudophakic OA patients ($n = 11$) had a mean increase in ACD of +38 μ m. There were significant increases in systolic, diastolic, and mean BP, as well as in IOP in the overall patient group. BP and IOP were significantly increased in each of the two major diagnostic groups as well. The increase in IOP for the three ACS patients with past LPs was on average the same as for the rest of the AC group (6 mm Hg). Because PP includes both BP and IOP, the rise in these two parameters was parallel enough that there was no significant change in mean or diastolic PP. There was, however, a significant increase in systolic PP overall and in OA patients. The IOP increase was significantly greater in AC patients than in OA patients (6.00 versus 4.25 mm Hg, $P = 0.004$). After the WDT, a significant increase in mean AL of 12 μ m occurred in the overall group, and mean AL increased significantly in both OA (9 μ m, $P = 0.01$) and AC groups (16 μ m, $P < 0.0001$) separately (Table 2).

Univariate regression analysis was conducted to determine parameters related to change in CT after WDT (Table 3). The associations were essentially unchanged whether we included all 88 eyes or only the 77 that had "good" or "fair" images (Table 3). Interestingly, percentage increase in IOP was not significantly associated with percentage CT increase ($P = 0.97$; Fig. 1). In the multivariate analysis for change in CT, none of the explanatory variables considered were significantly associated with absolute or percent CT change.

We then analyzed separately the 80 of 88 eyes that had at least a 2 mm Hg increase in IOP under the hypothesis that these would be persons who responded to the ingestion of water with a measurable IOP increase. Multivariate analysis for this responder group found that AC eyes had greater CT

increase than OA eyes at a borderline significance level ($P = 0.053$, Table 4). A larger increase in diastolic PP was also associated with greater CT increase. Among responders, a greater percentage increase (as opposed to absolute increase) in CT was associated with thicker CCT and greater increase in mean PP, with a borderline relation to greater shallowing of ACD ($P = 0.06$). Because there might have been interactions between diagnosis and other factors considered for this model, we expanded potential independent variables to include terms for interaction between diagnosis and several factors, including IOP. In this refined model, the more the IOP increased in AC eyes, the smaller was their CT increase (-1.25 μ m per mm Hg, $P = 0.01$, Fig. 2). By contrast, the IOP increase in OA eyes was not significantly associated with the change in CT (0.82 μ m per mm Hg, $P = 0.31$, Fig. 2). When the AC and OA regression lines for change in CT versus change in IOP were extrapolated to their y-intercept values (representing a hypothetical change in IOP of 0, Fig. 2), the difference between the two diagnosis groups was significant ($P = 0.003$), further suggesting that AC eyes responded differently to changes in IOP in the WDT than did OA eyes.

We also constructed multivariate models for change in IOP, both for all 88 subjects and for the responder group (patients with IOP rise of more than 2 mm Hg, Table 5). In both models, the higher the baseline IOP, the more the IOP rose. AC diagnosis was also significantly associated with greater IOP increase. Additionally, a greater increase in IOP was associated with a greater increase in AL; the mean IOP increase of 5.0 mm Hg corresponded to a mean AL increase of 12 μ m. Other variables that were also significantly associated with greater IOP increase were having a thinner baseline CT, diagnosed diabetes, and having a dilated pupil at the time of testing. Because those with AC had shorter AL than OA subjects, we suspected that AL and AC diagnoses might be surrogate parameters, leading to an underestimation of the significance of AC as a predictor of IOP increase. Indeed, when AL was excluded from the model, the AC group had an even more significant relationship to IOP increase ($P = 0.001$, for all participants and $P = 0.02$, for the 80 responders).

DISCUSSION

Our data do not support the hypothesis that the IOP rise after the WDT is fully explained by CT increase. First, we found no

TABLE 3. Change in CT after WDT, Univariate Analysis

Characteristic	All Participants, <i>n</i> = 88				Participants with Pre- and Post-WDT Images of Good/Fair Quality, <i>n</i> = 77			
	Change in CT, μm		% Change in CT		Change in CT, μm		% Change in CT	
	Regression Parameter (95% CI)	<i>P</i> Value	Regression Parameter (95% CI)	<i>P</i> Value	Regression Parameter (95% CI)	<i>P</i> Value	Regression Parameter (95% CI)	<i>P</i> Value
Diagnosis								
OAGS/OAG, R	0	0.07	0	0.19	0	0.19	0	0.41
ACS/AC/ACG	5.53 (−0.49, 11.54)		1.27 (−0.66, 3.21)		3.93 (−2.04, 9.90)		0.85 (−1.18, 2.87)	
Sex								
Male	−5.56 (−11.63, 0.51)	0.07	−1.50 (−3.44, 0.45)	0.13	−2.22 (−8.26, 3.82)	0.47	−0.68 (−2.72, 1.35)	0.51
Female, R	0		0		0		0	
Any glaucoma medication								
No, R	0	0.10	0	0.12	0	0.07	0	0.09
Yes	−4.99 (−11.00, 1.03)		−1.53 (−3.45, 0.39)		−5.33 (−11.20, 0.54)		−1.70 (−3.69, 0.28)	
Δ MPP, per mm Hg greater	0.30 (−0.09, 0.69)	0.13	0.10 (−0.02, 0.23)	0.10	0.23 (−0.16, 0.63)	0.24	0.08 (−0.05, 0.21)	0.23
SPP, per mm Hg greater	0.14 (−0.05, 0.33)	0.14	0.05 (−0.01, 0.11)	0.13	0.12 (−0.07, 0.31)	0.22	0.04 (−0.03, 0.10)	0.24
Δ DBP, per mm Hg greater	0.40 (−0.13, 0.94)	0.14	0.13 (−0.04, 0.30)	0.13	0.33 (−0.21, 0.87)	0.23	0.10 (−0.08, 0.29)	0.26
VF MD, per dB greater ^a	0.43 (−0.16, 1.03)	0.15	0.09 (−0.10, 0.28)	0.35	0.42 (−0.16, 1.01)	0.15	0.09 (−0.11, 0.29)	0.38
Δ DPP, per mm Hg greater	0.32 (−0.12, 0.75)	0.15	0.10 (−0.04, 0.24)	0.15	0.23 (−0.21, 0.68)	0.30	0.07 (−0.08, 0.22)	0.35
Δ MBP, per mmHg greater	0.32 (−0.12, 0.75)	0.15	0.11 (−0.02, 0.25)	0.11	0.27 (−0.16, 0.70)	0.22	0.10 (−0.05, 0.24)	0.19
CCCT, per 10 μm greater	0.55 (−0.22, 1.32)	0.16	0.19 (−0.06, 0.43)	0.13	0.78 (0.02, 1.53)	0.04	0.28 (0.03, 0.54)	0.03
Baseline CT, per 10 μm greater	0.18 (−0.08, 0.43)	0.17	0.04 (−0.04, 0.12)	0.35	0.20 (−0.11, 0.51)	0.20	0.04 (−0.07, 0.15)	0.46
Alpha agonist								
No, R	0	0.20	0	0.29	0	0.03	0	0.06
Yes	−6.24 (−15.76, 3.29)		−1.63 (−4.68, 1.41)		−10.85 (−20.36, −1.34)		−3.13 (−6.36, 0.10)	
Δ SPP, per mm Hg greater	0.15 (−0.10, 0.40)	0.23	0.06 (−0.02, 0.14)	0.15	0.12 (−0.11, 0.36)	0.30	0.05 (−0.03, 0.13)	0.24
Betablocker								
No, R	0	0.26	0	0.75	0	0.14	0	0.56
Yes	−3.96 (−10.96, 3.04)		−0.36 (−2.61, 1.88)		−5.00 (−11.74, 1.74)		−0.68 (−2.98, 1.62)	
Δ SBP, per mm Hg greater	0.14 (−0.11, 0.39)	0.28	0.05 (−0.03, 0.13)	0.18	0.12 (−0.12, 0.36)	0.32	0.05 (−0.03, 0.13)	0.24
Prostaglandin								
No, R	0	0.29	0	0.15	0	0.22	0	0.10
Yes	−3.29 (−9.43, 2.86)		−1.42 (−3.37, 0.52)		−3.73 (−9.73, 2.27)		−1.67 (−3.68, 0.33)	
Ethnicity								
White, R	0	0.71	0	0.93	0	0.63	0	0.97
Non-white	−1.24 (−7.85, 5.38)		0.10 (−2.01, 2.21)		−1.54 (−7.94, 4.85)		−0.04 (−2.20, 2.12)	
Age, per 5 y older	0.27 (−1.26, 1.79)	0.73	0.07 (−0.42, 0.55)	0.79	0.03 (−1.46, 1.51)	0.97	−0.01 (−0.51, 0.49)	0.96

CI, confidence interval; MPP, mean perfusion pressure; R, reference; Δ , change.^a All participants: *n* = 88; participants with pre- and post-WDT images of good/fair quality: *n* = 77.

TABLE 4. Change in CT after WDT, Participants with IOP Increase of More Than 2 mm Hg ($n = 80$), Multivariate Analysis

Characteristic	Change in CT, μm^*		% Change in CT†	
	Regression Parameter		Regression Parameter	
	(95% CI)	P Value	(95% CI)	P Value
Δ DPP, per mm Hg greater	0.47 (0.03, 0.91)	0.04	—	
Diagnosis				
OAGS/OAG, R	0	0.053	—	
ACS/AC/ACG	5.98 (−0.07, 12.03)			
CCT, per 10 μm greater	0.71 (−0.11, 1.53)	0.09	0.28 (0.01, 0.54)	0.04
Δ MPP, per mm Hg greater	—		0.13 (0.00, 0.25)	0.04
ACD, per mm greater	—		−1.25 (−2.57, 0.08)	0.06

Dashes indicate variables were not significant in the multivariate model.

* R-square = 0.1142.

† R-square = 0.1156.

statistically significant increase in CT either among all 88 subjects or in the OA group, although there was a significant increase in CT among the AC group. Hypothetically, it might be that only those persons whose CT increased have an IOP increase with the WDT, as suggested by the significant increase in CT in those with an IOP increase of more than 2 mm Hg. If this were the case, however, then we would have expected to see an association between absolute or percentage IOP rise and absolute or percentage CT change. Yet, this association was not present. There was a significant increase in IOP, 4.3 and 6.0 mm Hg 30 minutes after the WDT in the OA and AC groups, respectively. This IOP increase in the AC group was significantly greater than that in the OA group. These IOP increases are similar in magnitude to those seen in more recent studies that performed the WDT as we did.^{31–36} Thus, our failure to find a large increase in CT was not a result of failing to produce IOP elevation.

In part, our failure to find a substantial increase in CT may have resulted from the coincident increase in both BP and IOP in the WDT. CT is known to be dependent on age, AL, and PP (defined as BP minus IOP).¹⁴ Further support for the linkage between PP and CT was found in the present data. An increase in BP would likely be associated with an expansion of the intravascular volume of the choroid, leading to a thicker choroid.⁴⁴ At the same time, the greater the increase in the IOP, the more likely that the inside-out pressure differential across the choroid would thin it. In the OA group in this experiment, both BP and IOP increased, nearly in parallel, so that in most cases, PP was effectively unchanged, and the choroid neither significantly increased nor decreased in thickness. Interestingly, AC eyes had a significantly greater IOP rise than the OA eyes, as well as a greater increase in CT than OA eyes. This is the opposite of what would be expected from the observed IOP change alone, which would tend to cause thinning or allow less thickening of the choroid, all other factors being equal. AC eyes do illustrate that higher IOP increase tends to allow less CT increase (Fig. 2), so the expected relation does manifest itself to some degree. However, our data suggest that AC eyes have a tendency to greater choroidal expansion than OA eyes that outweighs what would be expected from the change in BP and IOP alone.

How much would the choroid have to increase in thickness to yield a short-term, 5 mm Hg increase in IOP? Using the geometry of a typical adult eye (eye volume of approximately 6200 μL as described by Silver and Geyer⁴⁵) and published pressure-volume data (equation 8 in Silver and Geyer⁴⁵), we estimated that to produce an IOP increase of 5 mm Hg from the average IOP of 15 mm Hg, the choroid would need to expand uniformly by approximately 10 μm , the exact value of

the expansion being dependent on the anteroposterior, horizontal, and vertical dimensions of the individual eye as well as the baseline IOP. This CT increase was calculated by estimating the volume change for the choroid as a three-dimensional solid occupying 75% of the ocular internal surface. Our subjects overall had a mean CT expansion of only 2.5 μm . This supports the conclusion that the IOP increase did not arise solely from a CT increase. The situation is more complex, however, because there are dynamic interactions between IOP, BP, CT, and AL (as measured by the IOL Master). These parameters theoretically could change in different temporal sequences. To understand fully how each factor contributes, we would need continuous measurement of each parameter instead of two measurements 30 minutes apart. The response of the scleral shell to a 5-mm rise in IOP would be an expansion that can be estimated from the known pressure-volume relation of human eyes.⁴⁵ This calculation yields an estimated AL increase of 10 μm , very close to the 12- μm increase observed in our study. The IOL Master measures AL from the cornea to the RPE, not to the sclera's inner surface. Therefore, if the sclera expanded as expected for a 5 mm Hg IOP rise, we would expect approximately a 10 μm longer eye.⁴⁵ If the choroid had become thicker, the AL as we measured should have increased less than 10 μm . This further supports the conclusion that CT increase does not fully explain the IOP rise from the WDT.

Because the IOP rise during the WDT seems not to have resulted from CT increase, it more likely resulted from decreased outflow facility.^{40,46} During the 1960s, it was shown by tonography that the outflow facility decreases after the WDT.⁴⁷ The extensive studies of the systemic effects of the WDT indicate that there is a dramatic increase in norepinephrine that drives BP upward.^{38,41–42} Water drinking is in fact used as a therapy in persons with orthostatic hypotension and dysautonomia. This rise in systemic α -adrenergic tone may lead to the increase in outflow resistance.

Others have suggested that choroidal expansion is associated with the IOP elevation in the WDT. A change in CT after WDT in OA patients was reported in measurements by ultrasonic biomicroscopy (UBM),³¹ but this technique has inherent limitations in resolution that make it unsuitable for such study. The reported baseline CT of 1000 μm and an increase of 200 μm during WDT by UBM are not consistent with SD-OCT measurements, whose axial resolution is substantially better. The living choroid is on average 250 μm thick in the posterior eye. Further, using the previously mentioned pressure-volume relationship of the eye, we determined that a 200- μm increase in CT would produce an IOP far above the systolic BP of the eye.⁴⁵

FIGURE 2. Scatter plots of change in intraocular pressure and change in choroidal thickness by diagnosis, participants with change in intraocular pressure greater than 2 mm Hg ($n = 80$). Regression lines are from the refined multivariate analysis of change in choroidal thickness for participants with change in intraocular pressure greater than 2 mm Hg ($n = 80$) taking into account the interaction of diagnosis with other factors, including intraocular pressure.

The fact that the rise in IOP after the WDT is a risk factor for development of initial OAG³⁷ may be because this trait is associated with the ease with which outflow facility is blocked. A tendency for outflow facility to decline more easily would tend to produce higher or more unstable IOP. Both higher mean and greater fluctuation in IOP are known to be associated with incidence and worsening of OAG.⁴⁸ Contrary to previous suggestions, however, we have not found that baseline CT is related to the degree of glaucoma injury,¹⁴ a finding corroborated by another report.⁴⁹

Our data show measurable differences between AC and OA eyes in both baseline CT and dynamic choroidal behavior during the WDT. CT was greater at baseline in AC eyes, possibly related to the known relation between smaller eyes and a thicker choroid.^{14,49} Increase in CT was greater in AC than in OA eyes after the WDT. Furthermore, AC eyes had a significantly greater increase in IOP than OA eyes. Finally, there was a decrease in ACD in AC but not in OA eyes, with the decrease in ACD in pseudophakic AC eyes being even greater than the decrease in ACD in the overall AC group. We speculate that the forward movement of an intraocular lens

TABLE 5. Change in IOP, Multivariate Analysis

Characteristic	All Participants, <i>n</i> = 87			Participants with Change in IOP > 2 mm Hg, <i>n</i> = 80		
	Change in IOP, mm Hg*		% Change in IOP†	Change in IOP, mm Hg‡		% Change in IOP§
	Regression Parameter	<i>P</i> Value	Regression Parameter	Regression Parameter	<i>P</i> Value	Regression Parameter
	(95% CI)		(95% CI)	(95% CI)		(95% CI)
IOP, per mm Hg greater	0.26 (0.12, 0.39)	0.0002	—	0.28 (0.16, 0.41)	<0.0001	−0.84 (−1.60, −0.08)
Δ AL, per 0.1 mm greater	5.04 (2.13, 7.95)	0.001	33.75 (14.14, 53.36)	6.49 (3.64, 9.34)	<0.0001	40.94 (23.40, 58.48)
Diagnosis						
OAG/OAG, R	0	0.002	0	0	0.03	0
ACS/AC/ACG	2.36 (0.90, 3.82)		9.32 (0.24, 18.40)	1.49 (0.15, 2.83)		7.81 (−0.47, 16.10)
Baseline CT, per 10 μm greater	−0.08 (−0.14, −0.01)	0.02	—	—		—
Diabetes						
No, R	0	0.04	—	0	0.02	0
Yes	2.20 (0.08, 4.31)			2.41 (0.32, 4.49)		12.95 (0.25, 25.66)
Dilated						
No, R	0	0.02	0	0	0.04	0
Yes	1.59 (0.23, 2.95)		9.36 (0.32, 18.40)	1.39 (0.04, 2.74)		10.40 (2.16, 18.64)
Age, per 5 y older	—		2.05 (−0.23, 4.32)	—		1.72 (−0.31, 3.75)

Dashes indicate variables were not significant in the multivariate model.

* R-square = 0.4485.
† R-square = 0.2705.
‡ R-square = 0.4758.
§ R-square = 0.4386.

would be greater than that of a native lens due to its lesser mass, producing greater ACD shallowing in pseudophakic AC eyes.

The greater tendency to choroidal expansion correlates these findings and may be related to the development of AC disease.²⁷ It has been clinically observed that intraoperative and postoperative choroidal expansion is more common in extreme cases of AC disease, such as nanophthalmos. Recent studies of AC eyes by UBM and anterior segment OCT show such significant choroidal expansion that it is visible as a clear space separating the choroid and sclera.^{50,51} Maul et al.¹⁴ reported that AC eyes had a thicker choroid than OA eyes, even after adjusting for other factors associated with CT, such as age, AL, and perfusion pressure. We hypothesize that choroidal expansion may contribute to the process of AC by causing an immediate increase in IOP.^{26–28} This would likely lead to increased outflow from the trabecular meshwork so as to restore the IOP toward normal, leading to a posterior to anterior pressure differential.^{26–28} As fluid leaves the anterior chamber under this pressure differential, aqueous volume in the anterior chamber would decrease, and the lens would move forward, narrowing the iris-lens channel and intensifying resistance to aqueous movement through the pupil (pupillary block).^{26–28} Hypothetically, in the AC eye, even anterior lens movement of a few micrometers would produce a rapid increase in the trans-iris pressure differential, bowing the iris forward to make contact with the meshwork.^{26–28} We observed suggestions of each of these steps in the AC eyes: more CT increase and IOP increase in AC than in OA eyes, as well as a decrease in ACD in AC but not in OA eyes. Thus, in the predisposed eye, a dynamic expansion of the choroid would contribute to a greater chance for symptomatic or asymptomatic AC. It is entirely possible that this mechanism is present in some AC eyes to a greater degree than in others.

Unfortunately, the WDT produces only a small change in CT, and some individuals actually had a measured decrease in CT despite an increase in IOP after the WDT. The WDT, therefore, may not be an ideal prognostic test to assess which eyes with narrow angles should receive iridotomy. Recently, we and others have found that the behavior of the iris may be a useful prognostic factor that identifies greater risk for AC.^{52,53} We are studying other ways to provoke changes in CT that are more clinically practical, postulating that those with greater CT increase would be more likely to develop AC. Ultimately, this will require longitudinal studies to demonstrate the usefulness of such an approach.

The limitations of our study include the possibility that the recruited subjects are not representative of all glaucoma patients; however, we have no reason to believe that they are different in any important way. Second, we measured the choroid in the posterior 6 mm, as this is the zone in which SD-OCT can best analyze it. In our assumptions and speculations, we considered the change in the posterior choroid to be a general change that would be proportionately distributed throughout the choroid. However, it is possible that only segmental changes in CT occur. We do not know at this time whether the CT change involves either the intravascular or extravascular compartment of the choroid, or both. Certainly, the extravascular compartment has no barriers to fluid interchange and the choroidal vessels interconnect over large zones. The advent of SD-OCT imaging of the choroid has opened approaches to study of this region, but the resolution will undoubtedly improve with further developments. Perhaps longer-wavelength light will provide better resolution of the CSI.

In summary, we found that eyes with AC have significant differences in the baseline and dynamic behavior of the choroid than OA eyes. These differences are consistent with

hypotheses linking choroidal expansion to the pathogenesis of AC disease. The lack of sufficient changes in CT during the WDT to explain IOP increase, particularly in OA eyes, suggests that the IOP elevation at 30 minutes results from other mechanisms.

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