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

We read with interest the article by Arora et al., “Choroidal Thickness Change After Water Drinking Is Greater in Angle Closure than in Open Angle Eyes.” It captured our attention because of its clinical relevance and because it extends the compelling evidence regarding the clinical usefulness of the water drinking test (WDT) in glaucoma management, which recently merited an editorial in another journal. Our group and others have been studying this stress test for the past decade and we are pleased to read that another group not only confirmed findings from our recent publications, but also added innovative information to the field, despite some minor methodological differences. As their main result, Arora et al. reported that the WDT resulted in a significant increase of the mean choroidal thickness (CT) in the eyes with angle-closure glaucoma (ACG) and among subjects whose intraocular pressure (IOP) rose >2 mm Hg (defined as “responders”), but not in eyes with open-angle glaucoma (OAG) or in the entire sample pooled together. Their observation that all responders experienced an increase in mean CT confirms our previous results, in which all eyes analyzed met their definition of responders, despite a small-time lag between the two events—that is, the mean maximum IOP increase occurred on average 15 minutes after the maximum CT increase.

Nevertheless, it is important to emphasize that even though Arora et al. confirmed in part our previous report, the two studies had substantial differences in methodology. We believe these differences should be identified and clarified in order to remind the journal readership that results of studies performed by different groups on the same topic may appear similar or contradictory depending on key methodological differences and definitions easily overlooked by those who do not critically scrutinize the different studies. Several of these issues are present in the current publication.

Our study included only patients with OAG, whereas the Arora et al. study included a mixed sample in which 54% of the eyes had OAG. Moreover, they included OAG and ACG suspects without specifying the proportion of suspected cases. It is possible that the group of glaucoma suspects may be contaminated with normal eyes, which have a physiologically functional trabecular meshwork, as opposed to eyes with established disease and impaired trabecular function.

The authors employed relatively novel imaging technology for choroidal thickness measurement (spectral domain optical coherence tomography, SD-OCT), which provides images of the retina and choroid with much higher resolution than the technique we employed at that time (oculr ultrasonography, OUSG). The resolution of OUSG is not as good as that of SD-OCT and this may have affected the accuracy of our measurements. Nevertheless, our study used a control group that did not undergo the WDT and had masked serial IOP measurements as a means to define the repeatability of the technique. Arora et al. did not include a control group and appear to have had issues with CT measurements, given the difficulty in defining the choroidal posterior boundaries (choroidal-scleral interface) as they described in the “Methods” section.

Their measurements were performed in the macular region (6.0 × 6.0 mm from the fovea) while we measured the estimated CT in a location corresponding to the equatorial zone of the globe. We opted to perform measurements in the equatorial zone, as this is the site where clinically choroidal detachments are most commonly seen and hence may be more susceptible to disturbances in thickness and volume. It has been shown that retinal thickness does not exhibit significant diurnal variation and is relatively stable in physiologic states. On the other hand, there is a circadian rhythm of choroidal thickness variation even among normal subjects.

We had many concerns with regard to how the WDT was performed in the study by Arora et al., as it appears to differ meaningfully from what our group and others have been doing. For instance, we ask patients to refrain from ingestion of fluids at least 4 hours prior to the test (which was not clarified in their study methodology); we ask patients to drink the water in a short period of time (less than 5 minutes)—instead of 15 minutes; and we perform IOP measurements at baseline, 15, 30, and 45 minutes after water ingestion, while Arora et al. measured the IOP only twice: before water ingestion and 30 minutes afterwards. Their IOP measurements (which they called “peaks”) were technically measurements taken 15 minutes after water ingestion only. Therefore, it is possible that they may have missed a significant proportion of IOP peaks and this may also explain why so many eyes were deemed “nonresponders” in their study, which in our experience is very uncommon among glaucomatous eyes. The time lag between CT expansion and IOP rise should be taken into consideration, as we did in our study, and is supported by a recent publication from another group.

Arora et al. appear not to have read our article thoroughly, as they stated incorrectly that “The reported baseline CT of 2000 μm and an increase of 200 μm during WDT by UBM are not consistent with SD-OCT measurements, whose axial resolution is substantially better” First, we did not use UBM, but rather OUSG. Given the inability of OUSG to differentiate the choroidal from retinal tissues under normal conditions, and assuming that retinal thickness is stable, we clearly stated in our article that, “During the scans, the choroidal space was measured between the echographic peaks of the retina and sclera using the peaks detected by the A-scan. Since both tissues are rigid and constant, any changes in this area were considered to be due to choroidal expansion.” Therefore, we never mentioned a mean CT of 1000 μm as the authors inaccurately reported. This is the measurement of the combination of all retinal layers, choroid, and sclera in the equatorial region of the globe. In fact, Esmaeelpour et al. showed in 3-dimensional CT maps that at a single time point, CT varies significantly in different areas of the posterior pole, being particularly thicker in areas farther from the fovea. The authors reported an increase in thickness of approximately 1500 μm inferior to the center of the fovea, compared with subfoveal CT using a high-resolution SD-OCT with 7-μm axial resolution.

Finally, Arora et al. stated that our finding of a 200-μm increase in CT during the WDT using “UBM” is unrealistic, as they reported that “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.” This brings to mind several questions: Would it be worth presenting these calculations to the readership, as we are interested in how the authors estimated the variation in the volume of the eye—named “delta V” in the Silver and Geyer paper—based on
cross-sectional measurements taken in a single area of the globe? In the cited reference from Silver and Geyer,\textsuperscript{15,16} despite the title "Pressure-Volume Relation for the Living Human Eye," their equation was based on mathematical modeling—more precisely, least-squares fitting of ocular rigidity coefficients regressed against IOP of ocular rigidity data from different authors—following numerous assumptions and not an actual experimental study. In fact, the authors pointed out in their paper that there was very large variability in the least-squares fitting of modified rigidity coefficients against IOP from different authors (refer to Fig. 1 of their article) and acknowledged that "Several caveats are important concerning the applicability of the new pressure-volume relation. The valid intraocular pressure range spans 8 to 61 mm Hg, since that is the pressure range corresponding to the available rigidity coefficient data." We would be interested to know how the authors calculated changes in ocular volume—which are required for Silver and Geyer's equation—based solely on changes in the average CT in a 6-mm width location within the macula. One problem suggesting that this model is not applicable to the current discussion is that the circadian variation in CT in normal subjects in about 20\textsuperscript{m}.\textsuperscript{15,16} Based on the same equation Arora et al. employed, regardless of its numerous limitations and assumptions, we calculated that a 20-\textmu m increase in CT would correspond to an IOP of 40 mm Hg. We do not usually see pressures that high in normal subjects even during 24-hour monitoring. Moreover, the CT and its changes are not the same throughout the globe,\textsuperscript{17} which would require more robust equations to estimate the relationship between changes in IOP relative to changes in CT in the globe. We acknowledge that our OUSG measurements were less precise than those from SD-OCT; nevertheless, the findings of Arora et al. do not invalidate our results and the example they used to contest our findings based on the work of Silver and Geyer is inadequate and unrealistic.

In summary, we congratulate Arora et al. for shedding light on a topic that is receiving increasing attention. By using new imaging technologies, they have confirmed previous reports and theories regarding the relationship between choroidal thickness and angle closure previously described by Lowe\textsuperscript{19} and Kirsch\textsuperscript{20} and which have long been overlooked. Also, we appreciate the opportunity to clarify differences between our studies, their methodology, and conclusions.

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