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Re: Melgarejo et al.: Glaucomatous optic neuropathy associated with nocturnal dip in blood pressure: findings from Maracaibo Aging Study (*Ophthalmology*. 2018;125:807-814)

TO THE EDITOR: We read and analyzed with great interest the article by Melgarejo et al.[1] The authors have conducted the study to determine whether an average nocturnal low blood pressure (BP) or an extreme dip in nocturnal BP is associated with an increased risk of glaucomatous damage in Hispanics. To date, an increased intraocular pressure (IOP) is the only modifiable risk factor in preventing and controlling glaucoma progression. It is obviously a novel effort to find out a new modifiable risk factor that may open a new therapeutic approach to prevent glaucoma progression.

However, we have several questions. First: Can a single episode of an extreme dip in BP cause optic nerve fiber damage? For an individual, does BP follow a fixed diurnal pattern? In the current study, the BP was only monitored for 24 hours. Therefore, the association found in this study might be coincidental. Pillunat et al[2] noted in their study that the major disadvantage of their study as well as other epidemiologic studies is the cross-sectional design, where BP is only measured during 1 day and night, whereas visual field defects or glaucoma develop over time.

Second, although the IOP was within the normal range in this study population, how will we be able to rule out the role of large fluctuations or morning peaks of IOP in these cases? Previously, many studies have shown that in patients with an IOP in the normal range, large diurnal fluctuation in IOP was an independent risk factor for development and progression of glaucoma.[3-5] These studies have also noted that in most of the patients, IOP peak occurred outside of office hours. Although IOP was selected as a confounding factor in the current study, the diurnal fluctuation of IOP, which is an important risk factor for glaucoma was not taken into consideration.

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REPLY: We thank Paul et al for their comments regarding our article.[1] To address their concerns, large, longitudinal studies collecting data on both ambulatory blood pressure monitoring (ABPM) and ophthalmological assessment (intraocular pressure, visual field testing, etc.) are needed. Previous longitudinal ABPM studies demonstrated that the dipping status of an individual is not necessarily constant or even repeatable. Based on reports from the Spanish ABPM registry and the Study on Ambulatory Monitoring of Pressure and Lisinopril Evaluation (SAMPLE), the dipping pattern of repeated ABPM records changed in 24% to 40% of subjects.[2,3] This inconsistency poses a limitation for cross-sectional and longitudinal studies that aim to assess the relationship between BP dipping status and ocular or systemic conditions.

The relationship of intraocular pressure variability, including circadian rhythms and long-term fluctuations, to the risk of glaucoma onset and progression is a key point that is not yet fully understood. We agree with Paul et al that longitudinal intraocular pressure data that include variations within and between days would help to elucidate this association. However, we did not collect such data as part of our cross-sectional study. We appreciate their comments.

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Re: Hou et al.: Integrating macular ganglion cell inner plexiform layer and parapapillary retinal nerve fiber layer measurements to detect glaucoma progression

(*Ophthalmology*. 2018;125:822-831)

TO THE EDITOR: We read with interest the article by Hou et al.[1] Attempts to integrate both parapapillary retinal nerve fiber layer (RNFL) and macular ganglion cell inner plexiform layer (GCIPL) guided progression analysis (GPA) results, and to investigate the temporal relationship between them are interesting and necessary for understanding glaucoma progression.

However, we would like to make a few comments on the methodology by which authors defined the spatial correspondence between progressive RNFL thinning and progressive GCIPL thinning to evaluate the temporal relationship. The definition of the zone simply in both superior and inferior hemiretina, as shown in this study, may be limited. How did authors assess spatial correspondence if the glaucoma progression was to occur in >1 place in GPA maps? We would like to discuss this in the presented figure in the main article.

The authors presented Figure 1A as the progressive GCIPL thinning at the superotemporal (ST) macula detected before progressive RNFL thinning at the ST optic disc region. Looking at the RNFL thickness maps, RNFL thinning at the ST optic disc region already existed at baseline and it can be hard to assert progression was detected GCIPL first, only with GPA programs. In 2013, the RNFL progression was also found in the inferoinferior region with RNFL GPA, not in the ST region. How did the authors assess spatial correspondence in this case? Each of several progression location needs to be analyzed separately.

The authors presented Figure 1B as the progressive RNFL thinning preceding progressive GCIPL thinning. However, in the case of superior hemiretina, progression was detected simultaneously from both RNFL and GCIPL GPA from January 2013. In the case of inferior hemiretina, the parapapillary sectors could be separated into macular vulnerability zone and inferoinferior region according to Hood et al.[2-4] In the inferoinferior sector, progression was detected only on RNFL GPA. Progression detected in the inferior hemiretina's GCIPL GPA would not be associated with the inferoinferior parapapillary region shown on RNFL GPA.

Although it is difficult to analyze this with methodologic complexity, it would be more helpful for the more sophisticated analyses that individual progression location would be analyzed separately, and the spatial correspondence would be determined between anatomically connected areas.

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REPLY: We thank Drs Lee and Park for their interest in our work.[1] We defined spatial correspondence between progressive retinal nerve fiber layer (RNFL) thinning and progressive ganglion cell inner plexiform layer (GCIPL) thinning whenever superior or inferior, progressive RNFL and GCIPL thinning was observed in the guided progression analysis (Methods, p. 824, Evaluation of Spatial Correspondence in Glaucoma Progression),[1] We adopted a less sophisticated approach to define spatial correspondence because of the limited scan area constrained by the OCT scan protocol for RNFL/GCIPL thickness analysis. Whereas the RNFL thickness was analyzed over the 6×6-mm optic nerve head region, the macular GCIPL thickness analysis was limited to a relatively small elliptical annulus, with inner vertical and horizontal axes of 1.0 and 1.2 mm, respectively, and outer vertical and horizontal axes of 4.0 and 4.8 mm, respectively.