Reply:

M.L. Hibert, Y.I. Chen, N. Ohringer, L.R. Wilbur, N.K. Waheed, J.S Heier, M.W. Calhoun, P.J. Rosenfeld and J.R. Polimeni

AJNR Am J Neuroradiol 2022, 43 (12) E62-E63
doi: https://doi.org/10.3174/ajnr.A7717
http://www.ajnr.org/content/43/12/E62

REPLY:

We thank Ribarich et al for their interest in our work and thank the editors of *AJNR* for giving us the opportunity to respond to this letter. Dialogues such as this are an important part of healthy scientific discourse and progress, and we hope that our responses can help clarify several points of our article and thereby help strengthen our study.

Ribarich et al noted that our patients with age-related macular degeneration (AMD) and control groups were not perfectly age-matched, but this was addressed in our description of the statistical analysis performed. We used a generalized estimating equations (GEE) method and explained that age was included as a variable in our model as well as in the calculation of post hoc comparisons if it was statistically significant. Table 1 identifies the comparisons for which age was statistically significant and was, therefore, included in the GEE model.

Ribarich et al also noted that our article did not report cardiovascular disease burden in the study population. This is true, though it was not the focus of the article because cardiovascular risk is known to be associated with AMD;[1-4] our focus remained on the potential effects of that association by examining the vascular condition as it related to disease progression. The differences between the population with AMD and the similarly matched controls are interesting and need to be explored further.

Nevertheless, as part of this discussion, it is important to maintain the distinction between linear flow and volumetric flow. It is understood that linear flow (velocity) in the ophthalmic artery (OA) increases with age, as Ribarich et al state. An increase in linear flow is thought to be the result of decreased volume. The volume is decreased due to atherosclerotic changes, and the linear flow (velocity) increases from an otherwise unchanged pressure system. Because the patient group with AMD is, on average, slightly older than the control group, the age difference could be expected to yield a small linear flow increase in patients with AMD; however, it is not thought to account for the statistically significant differences reported. The more interesting takeaway is the trend test plot (presented in Figure 4 of our published article) demonstrating that the association between the rate of decline in OA volumetric flow with AMD disease progression is statistically significant. This finding demonstrates the potential for decreased ocular perfusion to affect the AMD process, perhaps in those patients who are genetically predisposed.

Regarding the question of our reported measurement variability, we acknowledged the limitation of estimating variability in 1 subject, and we agree that additional measurements would be valuable to improve this estimate. As Ribarich et al note, the within-subject variability that we estimated was still substantially lower than the difference between groups. We note here that as indicated in the discussion section of our article, our phase-contrast MRA measurements were remarkably similar to those reported in the prior study of Ambarki et al,[5] who reported a resistance index of 0.68 (SD, 0.08) in the OA compared with our value of 0.70 (SD, 0.10) in similarly aged control subjects. These findings provided us with additional confidence in the quantitative validity of our measurements.

Ribarich et al noted that 2 patients with AMD had only 1 eye affected by AMD and suggested a new analysis of our data that may be helpful to understand whether vascular changes occur before or after the development of AMD. This observation does not appear to be a criticism per se, and we agree that this suggested analysis based on $n = 2$ subjects should not be overinterpreted. In reviewing our data for this response letter, we realized that 1 of the eyes that we reported was excluded from analysis due to motion and not due to diagnosis, and we apologize for the misstatement in our article. Thus only 1 patient in our group was diagnosed with AMD in a single eye. We reviewed our data from this 1 patient, and we can confirm that the trend that we reported is also seen in this patient: The OA of the healthy eye has a volumetric flow rate of 13.3 mL/min and a resistance index of 0.77, while the OA of the AMD eye has a volumetric flow rate of 2.9 mL/min and a resistance index of 0.86. Again, we should not overinterpret this $n = 1$ analysis, but it is reassuring.

Finally, Ribarich et al noted that the proportion of excluded patients was remarkable, and that a "majority" of measurements were discarded due to motion; however, this statement is incorrect and may be a misunderstanding. We apologize if this was unclear in our article. Data were included from 21 of 24 patients with AMD, and from 12 of 13 controls. We excluded approximately 30% of OAs from patients with AMD and 25% from controls, and far fewer ICAs were excluded in both groups. We agree that there was an unfortunately large number data sets that could not be analyzed due to motion artifacts, but fortunately, the number of data sets included in our analysis was still sufficiently high due to the large overall number of volunteers. We note again that all volunteers were cooperative; however, these were all older individuals, and our 7T MR imaging scanner is somewhat less comfortable than clinical MR imaging scanners due to the long bore size and the tight-fitting radiofrequency head coil, which contribute to a less pleasant patient experience, increasing the potential for motion.

Again, we are glad to have the opportunity to clarify these points, which we hope will help further strengthen our article. We hope that Ribarich et al agree that all points that they have raised have been fully addressed, and there is no evidence of "significant misinterpretation" of the data reported in our article. We agree with Ribarich et al that this is an important topic that warrants further investigation that will build on our findings to better understand the role of abnormal OA flow in AMD.

REFERENCES

1. Pennington KL, DeAngelis MM. **Epidemiology of age-related macular degeneration (AMD): associations with cardiovascular disease phenotypes and lipid factors.** *Eye Vis (Lond)* 2016;3:34 CrossRef Medline
2. Hyman L, Schachat AP, He Q, et al. **Hypertension, cardiovascular disease, and age-related macular degeneration.** *Arch Ophthalmol* 2000;118:351–58 CrossRef Medline
3. Klein R, Klein BEK, Tomany SC, et al. **The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam eye study.** *Ophthalmology* 2003;110:636–43 CrossRef

http://dx.doi.org/10.3174/ajnr.A7717

4. Thomson RJ, Chazaro J, Otero-Marquez O, et al. **Subretinal drusenoid deposits and soft drusen: are they markers for distinct retinal diseases?** *Retina* 2022;42:1311–18 CrossRef Medline
5. Ambarki K, Hallberg P, Jóhannesson G, et al. **Blood flow of ophthalmic artery in healthy individuals determined by phase-contrast magnetic resonance imaging.** *Invest Ophthalmol Vis Sci* 2013;54:2738–45 CrossRef Medline

M.L. Hibert
Athinoula A. Martinos Center for Biomedical Imaging
Massachusetts General Hospital
Charlestown, Massachusetts

Y.I. Chen
Athinoula A. Martinos Center for Biomedical Imaging
Massachusetts General Hospital
Charlestown, Massachusetts
Department of Radiology
Harvard Medical School
Boston, Massachusetts

N. Ohringer
Athinoula A. Martinos Center for Biomedical Imaging
Massachusetts General Hospital
Charlestown, Massachusetts

L.R. Wilbur
OcuDyne, Inc
Roseville, Minnesota

N.K. Waheed
New England Eye Center
Tufts Medical Center
Boston, Massachusetts

J.S Heier
Ophthalmic Consultants of Boston
Boston, Massachusetts

M.W. Calhoun
OcuDyne, Inc
Roseville, Minnesota

P.J. Rosenfeld
Department of Ophthalmology, Bascom Palmer Eye Institute
University of Miami Miller School of Medicine
Miami, Florida

J.R. Polimeni
Athinoula A. Martinos Center for Biomedical Imaging
Massachusetts General Hospital
Charlestown, Massachusetts
Department of Radiology
Harvard Medical School
Boston, Massachusetts
Harvard-MIT Division of Health Sciences and Technology
Massachusetts Institute of Technology
Cambridge, Massachusetts