Author's response to reviews

Title: Frequency Doubling Technology, Optical Coherence Technology and Pattern Electroretinogram in Ocular Hypertension

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Author's response to reviews: see over
Dear Ms April Gerobin,
here enclosed you will find a point-by-point replay to the reviewers’ comments and the second revision version of the manuscript entitled: “Frequency doubling technology, optical coherence technology and pattern electroretinogram in ocular hypertension”, M. Cellini, P.G. Toschi, E. Strobbe, N. Balducci, E.C. Campos.

Reviewer 1: Christopher Bowd

1. In the Abstract, the authors should include the values for both the OH and healthy groups. The phrase “OCT showed a very significant thinning of RNFL in the superior quadrant (130 +/- 10.02, p < 0.011)” is not informative because the reader does not know the measurement from the other experimental group.

We changed the sentence adding the information required: “In patients with OH, OCT showed retinal nerve fiber layer (RNFL) thinner than in control group in the superior quadrant (130.16±10.02 vs 135.18±9.27 µm, respectively ; p<0.011) and inferior quadrant (120.14±11.0 vs 132.68±8.03 µm; p<0.001). FDT showed a significantly higher pattern standard deviation (PSD) (3.46±1.48 vs 1.89±0.7 dB; p<0.001).”
2. In the Abstract, the criteria used to define OH and healthy should be included, not the final measurements from each group.

We corrected the previous sentence with this: “Fifty-two patients with OH (24 men and 28 women, mean age of 56±9.6 years) with an intraocular pressure (IOP) > 21 mmHg and fifty-two control patients (25 men and 27 women, mean age of 54.8±10.4 years) with IOP < 21 mmHg, were assessed.”

3. Abstract methods, line 4 “perimetric”, not “parameteric”.

We corrected this term.

4. Some of the references are not ideal. The authors should try to cite source papers, rather than review papers, when making particular claims.

We replaced reference #7 (review paper) with this more appropriate reference (source paper): Blumenthal EZ, Williams JM, Wainreb RN. Reproducibility of nerve fiber layer thickness measurements by use of optical coherence tomography. Ophthalmology 2000;107:2278-2282.

5. Some of the claims are controversial. For instance, it’s not necessarily true that RNFL alterations precede optic disc and visual field defects. This observation might very well be due to the techniques used for testing. Similarly, there are studies that show that SWAP is not more sensitive to SAP.

We corrected this claim: “Glaucoma is an optic neuropathy characterized by the progressive loss of ganglion cells and consequent visual field alterations.” with this: “Glaucoma is an optic neuropathy characterized by the progressive loss of ganglion cells and visual field alterations.”

Moreover, we corrected this claim “The qualitative analysis methods currently available are standard achromatic perimetry (SAP) and the more sensitive short wavelength automated perimetry (SWAP)” with this: “The qualitative analysis methods currently available are standard achromatic perimetry (SAP) and short wavelength automated perimetry (SWAP)”

6. Need to state how the optic disc/RNFL were assessed. Exam? Photographs?

We specified how we assessed optic disc/RNFL: “The patients all had normal visual acuity (VA), a normal optic disk (in particular, with no sign of diffuse thinning or focal narrowing or notching of the neuroretinal rim, hemorrhage, cupping or visible or progressive changes in the fiber layer on
ophthalmoscopic examination with a +78 diopter lens) and mean defect (MD) and pattern standard deviation (PSD) perimetric indices of less than 1.5 dB (0.28±1.1 and 0.65±0.4, respectively).

Also, the authors need to specifically define a normal visual field.

We defined a normal visual field adding this sentence: “A normal visual field was defined by the absence of each of these responses: a cluster of 3 points lower than P<5% or a cluster of 2 points lower than P<1% on a pattern deviation plot, or PSD with P<5%.”

7. The authors should not necessarily compare their results for the flash-PERG with studies using the steady-state PERG. If they wish to do this, they should point out the differences.

As the reviewer correctly says, the references # 28, 42 and 43 relate to studies were steady-state PERG was employed. So we corrected the previous sentence, with this: “Finally with transient PERG, a reduction in P50 amplitude was found in 78% of OH patients, with a sensitivity of 52% and a specificity of 77%, whereas an increase in latency was found in only 62% of cases. These data are similar to findings of previous studies, were steady-state PERG was employed.”

8. PERG amplitude (at least steady-state PERG amplitude) is notoriously affected by IOP. Therefore, the comparison between eyes with IOP # 21 mmHg and those with normal IOP is not really fair, as the difference likely is not due to early disease. I’ll leave this issue up to the Editors to address.

We calculated linear correlation between IOP and PERG amplitude. In OH group we found an inverse correlation between IOP and PERG amplitude (r=-0.28 and p=0.04, Pearson test). Instead, in control group we did not find any correlation (p=0.79).

To better specify this feature we added: “PERG amplitude is inversely related to IOP in OH group [Colotto A, Falsini B, Salgarello T et al. Transiently raised intraocular pressure reveals pattern electroretinogram losses in ocular hypertension. IOVS 1996; 37 (13): 2663-2670]. So, we could suppose that PERG amplitude difference between OH and control group could be in part due to different IOP values and not to early disease.”
Major Compulsory Revisions

1. The authors use statistics to compare FDT, OCT and PERG measurements between the OH and healthy groups, but they stop at that. Knowing the measurements are different between these groups does not say anything about the relative classification (i.e., OH versus healthy) ability among instruments. The authors need to compare ROC curve areas, perhaps using the method of Delong and colleagues (DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-45). That way, they can say something like “OCT measured inferior quadrant RNFL thickness and FDT PSD discriminated between OH and healthy eyes better than PERG amplitude (p=0.0x and 0.0x, respectively)”. As it stands, we do not know if that’s the case.

We compared ROC curve areas using the method of Delong and colleagues. We add this sentence in the results section: “OCT measured inferior quadrant RNFL thickness and FDT PSD discriminated between OH and healthy eyes better than PERG amplitude (p=0.04 and <0.0001, respectively). Moreover, FDT PSD discriminated between OH and healthy eyes better than OCT measured inferior quadrant RNFL thickness (p=0.01).”

We specified in the methods section the test used for the statistical analysis and this sentence was added: “To compare ROC curve areas Delong test was used”.

Also it would be good to know which of the ROC curve areas differed significantly from chance (i.e., were significantly greater than 0.50). This can be accomplished by showing that the 95% confidence intervals of the ROC curve areas (which should be included in Table 3) do not include 0.50.

We included in the table 3 the 95% confidence intervals of the ROC curve areas.
The authors also should compare sensitivities at fixed specificities (values obtained from the values making up the ROC curves) among instruments. It’s possible to do this using a McNemar’s test (and possibly other techniques). This comparison is not as important and probably can be considered discretionary.

We think that this comparison is not as important and that it would make the results more complex.

Reviewer 2: Luis Pablo

1. In the abstract section the authors wrote “normal optic disk and normal parametric indices”, I assume is a mistake and should say “normal perimetric indices”

That was a mistake and we corrected the term “parametric” in “perimetric.”

Yet there is no indication throughout the text of what parameters they used to consider a field as normal.

See answer number 6 to reviewer C.B. We added this sentence: “A normal visual field was defined by the absence of each of these responses: a cluster of 3 points lower than P<5% or a cluster of 2 points lower than P<1% on a pattern deviation plot, or PSD with P<5%.”

This is a major issue in this paper, the OH group was composed only by OH without any perimetric defect?

Yes, as we explain in the method section, the OH group was composed by patients with IOP> 21 mmHg without any visual field or optic disc defect.

2. In the tables the authors only offer information about means, SDs and statistical significances. Sometimes this information could provide a bias due to the lack of ranges, maximums and minimums.
We think that means, SDs and statistical significances are the most important information that better summarize the data under examination. Ranges, maximums and minimums are less important from a statistical point of view and maybe if we insert also these data in the tables, the reading of the tables would be more artificial.

However, if you feel appropriate and necessary these data, we will insert them in the tables.

Also I miss a multivariate test for the statistical analysis.

Please, see answer #1 to previous reviewer in the section “Major Compulsory Revisions”

3. Conclusions stated that PERG is a useful technique although in this study ROC curves showed values close to 0.5.

To better clarify this statement, we added 95% confidence interval of the ROC curve areas in the table 3, where it is possible to observe that PERG amplitude shows the 95% confidence interval between 0.552 to 0.746, so it is slightly above to 0.5.

I hope that the new revision version it is now O.K. for publication.

Sincerely yours

Dr. Mauro Cellini