Author’s response to reviews

Title: Instability of 24-Hour Intraocular Pressure Fluctuation in Healthy Young Subjects: a prospective, cross-sectional study

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Author’s response to reviews: see over
Instability of 24-Hour Intraocular Pressure Fluctuation in Healthy Young Subjects: a prospective, cross-sectional study

To Reviewer #1

Major Compulsory Revisions,

1) The methods of the study should be more detailed and higher attention should be paid on relevant topics such as masking, allowed intervals around the time-points, evaluation of achrophase. Methods, “The same clinician measured the IOP, but the IOP values recorded during the previous consultations were completely masked to the clinician”. In general, masking process is extremely rigorous and it reflects the quality of a study. Here, it is extremely vague.

: Thank you for a thoughtful review. We have added more information into the methods section as follows: "A single clinician measured the IOPs. To avoid bias, the previous IOP values were completely masked to the clinician and the statistical analysis was performed by an independent person."

2) References, Ref [1-10]: this is extremely partial. Relevant papers by at least two groups (Konstas, Orzalesi-Rossetti-Fogagnolo) were not mentioned.

: Thank you for suggestion of these good references. We have cited them in the revised manuscript.

3) A careful revision by a native-speaking English is mandatory; just few examples: although, partake; Abstract: “wonderful agreements”

: Our manuscript has been proofread by a professional English editor. Thank you for your recommendation.

Discretionary Revisions,

1) “Regarding MOPP, which is similar to IOP, showed a poor fluctuation agreement”: please rephrase.

: That sentence has been changed as suggested. Thank you for your careful comment.

2) “To characterize the circadian IOP pattern”: I would use more caution on this sentence; I would just refer to “fluctuation”, instead of “pattern”.

MS: 720233391321235
3) The lack of control on the use of caffeine, alcohol, and on quantity/quality/time of sleep surely influenced the results of this paper, and deserve a detailed discussion. The curves of figure 1 are likely the consequences of these concepts.

To Reviewer #2

1) Major. It is not clear what it is compared in the study. I see the p-values in the Tables but I don’t understand what they refer to. Also, it is not mentioned what statistical test has been used for comparisons (and what are comparisons). I think that providing the ICC with CI is not sufficient to the reader: something related to the variability extent and its statistical significance should be presented. Probably ANOVA is the best test to address the issue.

To Reviewer #3

2) Minor. Was CCT measured? Was there a sleep/wake time? It would be interesting to see whether variability was higher during the wake time rather than during the sleep time. In the abstract there’s the term wonderful agreement. Please change to excellent if appropriate.

To Reviewer #3

Actually, we did not measure the fluctuation of central corneal thickness. Although some studies reported that the 24-hour changes in corneal viscoelasticity do not seem to account for the IOP rhythms, the corneal biomechanical properties may actually influence the 24-hour IOP rhythm. It would be the topic of our further study and the description has added to the discussion section. Also regarding sleep, we did not record the exact sleep time in the present study. In addition, our manuscript has been proofread by a professional English editor. Thank you for comments.
Major Compulsory Revisions,

1) Actually there is no consensus about the role of IOP fluctuation for developing POAG from OHT or for POAG progression. Several randomized clinical trials (OHTS, EGPS, EMGT) failed identifying IOP fluctuation as an independent risk factor for progression. However, other studies identified fluctuation as an important and independent risk factor for POAG progression (for example, Asrani and coll.; Konstas and coll, Journal Ocul Ther Pharmacol Ther 2012). Please expand this topic and insert proper literature references.

: Thank you for your careful advice. The detailed description has added to the background section as follows: “There has been controversy about whether IOP fluctuations are an independent predictive risk factor for the progression of glaucoma. In previous studies, large fluctuations in diurnal IOP were independent risk factors for the progression of glaucoma [8,13], and in other studies, diurnal fluctuations in IOP itself were not independent risk factors [6,14]. Even though the IOP fluctuations are not a predictive or independent factors, there is a consensus regarding the importance of understanding circadian IOP profiles in glaucoma patients. However, in nearly all studies characterizing diurnal or circadian IOP patterns, there have been little or no data describing the repeatability of IOP patterns over time.”

2) Goldmann tonometer was used for sitting IOP measurements, while Tonopen-AVIA was used for supine IOP measurements. While it’s true that this doesn’t affect the slope of 24-hour IOP curve in single body positions, more data about the agreement between the two tonometers should be added, in consideration of higher supine than sitting IOP values found in the study.

: The data to compare IOP measurements of GAT vs. Tono-Pen AVIA have been added in Table 2. Thank you for your comment.

3) IOP and blood pressure fluctuations were analyzed in sitting and supine position over the 24-hour. However it would be useful to consider also a mixed curve, with sitting-IOP values during the day and supine-IOP values during the night. This would reflect closer the physiological IOP and blood pressure 24-hour curve, despite a possible systematic error due to the use of different tonometry techniques. Recent studies have shown the effect of different tonometry techniques on IOP postural change evaluation (discuss and add references).

: When the participants remained in a sleep laboratory and their sleep cycles were controlled, the sitting and supine IOPs are more suitable to be analyzed for day and night, respectively. In this investigation, the participants were not restricted in their sleep cycles in order to investigate the IOP/BP values in their real lives. Thank you for your careful advice.
4) Authors used Intra-Class Correlation Coefficient (ICC) to evaluate reliability of IOP and blood pressure measurements. ICC is typically used when there are a number of different interviewers, raters or assessors within the survey. It is defined as the proportion of total variance within data that is explained by variance between interviewers. Calculating IOP fluctuation as maximum-minimum IOP, authors caused an increase in data variance (for independent variables the Bienaymé formula says: \( \text{Var}(X-Y) = \text{Var}(X) + \text{Var}(Y) \)). I suggest authors to rename “IOP fluctuation” as “IOP range” and calculate IOP fluctuation as standard deviation of IOP measurements, a more stable index.

: Due to the terms “long/short-term IOP fluctuations,” which have been traditionally used in many literatures and routine clinical settings, it is supposed to be less confusable to the readers. And we computed the ICC values to determine the reliability of different IOP measurements. We deeply appreciate your thoughtful consideration and supportive advice.

5) Table 1, 2 and 3 should be revised. It would be interesting to see mean values of IOP, blood pressure and MOPP for every day of the study, so that data significance could have immediate impact on the reader.

: Table 1-3 have been improved and changed to Table 3-5. Thank you for careful comment.

6) Authors found higher supine than sitting IOP values in healthy young patients (\( p=? \)), in spite of the use of different tonometry techniques, while ocular perfusion pressure was quite constant both sitting and supine (\( p=? \)). A recent review by Quaranta and Coll, entitled “24-hour intraocular pressure and ocular perfusion pressure in glaucoma” (Survey of Ophthalmology, 2014) analyzed the topic in patients affected with glaucoma. Please add reference. Another recent paper by Quaranta and Coll. failed identifying a significant difference in IOP between day and night, in patients affected with OHT and POAG (IOP was measured during the day in sitting position with Goldmann tonometer and during the night in supine position with Perkins tonometer; article’s title: “Untreated 24-h intraocular pressures measured with Goldmann applanation tonometry vs nighttime supine pressures with Perkins applanation tonometry”, Eye 2010). Please compare with your results and add appropriate references.

: Thank you for suggestion of these excellent references. We have cited them in the revised manuscript.

7) A recent work by Aptel and Coll. analyzed reliability of 24-hour phasing in patients affected by
OHT and POAG. They found poor agreement between two 24-hour IOP curves performed at least 6 months apart. Please add reference and compare with your results.

: Thank you for suggestion of this good reference. We have cited it in the revised manuscript.

8) Graphs of IOP and blood pressure phasing in patient n. 6 should be substituted by more general graphs of the entire population of the study. Authors should graph maximum, minimum and fluctuation values for IOP and blood pressure during the days of the study for the entire population. This would give a better scenario of 24-hour parameters’ trend.

: The changed graph seems to be confusing for readers. Accordingly, the information has been added in table 1. We deeply appreciate your careful advice.

Minor Essential Revisions,
9) Please correct reference n.1 (typing error)

: Thank you for your comment. Actually, the revised manuscript does not include that reference.

To Reviewer #4,

1) I have found major problems in the small sample size and statistical analysis of the data.

: I agree with your opinion. Small sample size is one of the limitations of this study. We expect that our study could form one of the cornerstones for further studies. Thank you for your thoughtful consideration.

2) Methods are not completely clear (eg subjects come to clinic during nighttime, or sleep in the hospital, if it is the first case how long does it take to come to the hospital and how long before the subjects wake-up) Please give more detailed informations about 24-hour IOP assessment.

: The detailed information has been added to the method section. All participants were training as residents in various departments in our institute. We measured the parameters when they were on duty as residents in training over a 24 hour period in our institute. They stayed in the hospital but were not hospitalized. We did not restrain the daily lives of the participants during the study. Thank you for your careful consideration and good comment.

3) Please quote and discuss three papers of our group:


2. Konstas AG, Quaranta L, Mikropoulos DG, Nasr MB, Russo A, Jaffee HA, Stewart JA,


: Thank you for your recommendation of these good references. We have cited them in the revised manuscript.

4) Please give more detail insights on correlations between IOP and BP fluctuations during the 24-hour.

: In our study, the ICC values of BP fluctuations had an excellent agreement, although the ICC values of IOP fluctuations had a poor agreement. This implies that IOP and BP fluctuations can be positively, but not causally correlated. Systemic blood pressure is known to have a circadian rhythm, such as nocturnal BP reduction. However, in our study, it was not apparent. This might have been affected by the irregular sleep patterns of our subjects. We deeply appreciate your careful comments.

We deeply appreciate your careful consideration and wish our article to be accepted for publication in BMC Ophthalmology.

With Best Regards,

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