Author's response to reviews

Title: Biomechanical properties of the cornea measured with an Ocular Response Analyzer and its association with anterior segment parameters including corneal volume and anterior chamber volume

Authors:

ho sik hwang (huanghs@hanmail.net)
seh kwang park (bgnpark@gmail.com)
man soo kim Prof. (mskim@catholic.ac.kr)

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Author's response to reviews: see over
Reviewer's report

Title: Biomechanical properties of the cornea measured with an Ocular Response Analyzer and its association with anterior segment parameters including corneal volume and anterior chamber volume

Version: 1 Date: 1 February 2013

Reviewer: Ioannis Petropoulos

Reviewer's report:

Major Compulsory Revisions

1. Introduction, line 35. The authors should further explain what they define as “parameters have an uncertain correlation”. What is an uncertain correlation? Negative, positive, no correlation or controversial results?

Answer: “uncertain correlation” means “controversial correlation”. We changed the word as the reviewer’s recommendation.

These are applied at line 74.

2. Introduction, line 37. “Pentacam” is the commercial name of an anterior segment tomographer. Although an AST is usually termed as “Pentacam” amongst clinicians due to its wide use across Ophthalmology and Optometry, the authors should be accurate with terms in scientific writing and reporting. Also, as per the Ocular Response Analyser, details of the manufacturer should be given.

Answer: We change “A Pentacam” to “An anterior segment tomographer (ex. Pentacam)”. These are applied at line 76.

We added more details of the manufacture at line 58-59,113.

3. Introduction, lines 42-46, “Therefore, the aim of this study...really represent”
The aim(s) of the study should be clearly stated. Although this is the case for this study the authors could improve the text with shorter sentences and maybe by defining a primary and secondary aim.

**Answer:** We removed the rather vague sentence (“and to determine what the CH and CRF really represent.”) from the aim of the study. The other reviewer also recommended to remove the phrase from the aim of this study.

These are applied at line 82-85.

4. Introduction, lines 45-46 “and to...what they really represent”. Please re-define.

**Answer:** We removed the rather vague sentence (“and to determine what the CH and CRF really represent.”) from the aim of the study. The other reviewer also recommended to remove the phrase from the aim of this study.

These are applied at line 82-85.

5. Methods, general, the authors should add a few lines on how the technique was performed. Environment, experimental settings on the equipment etc.

Perhaps the authors could separate their methods in sections such as Subjects, Experimental procedure, Measurements, Statistical Analysis etc.

**Answer:** We added the sections in the methods. We added some sentences on how the technique was performed.

These are applied at line 119-124.

6. Methods, lines 72-75, although calculations are well explained they are repetitive e.g. “the average of P1 and P2 is the measure of IOP” and then “IOPg is only the average of P1 and P2”
Answer: We removed the repetitive sentence (“the average of P1 and P2 is the measure of IOP “) from the manuscript.

These are applied at line 115.

7. Methods, line 88. Please add results from Post-hoc analysis i.e. a short explanation on why P-value was maintained at 0.05.

Answer: We changed the sentence about p-value as following.

In consideration of multiple testing problem, a \( p \) value < 0.025 was considered statistically significant for two primary outcomes, CH and CRF.

These are applied at line 134-136.

8. Methods, line 116. “CRF was positively associated with the corneal thickness”

the authors state elsewhere in the text “because CRF is designed for maximum correlation.” Is this stating the obvious? Please elaborate.

Answer: It is obvious that CRF was positively correlated with the central corneal thickness, because CRF was designed for maximum correlation with corneal thickness.

These are applied at line 223-225.

9. Discussion, lines 151-153, please provide further evidence on why some contradict other? Sampling methods, participant status, disease vs. no disease?

Answer: This difference could be related to the small sample size in the previous studies or could represent ethnic variations in biomechanical properties. Chang et al included 63 Taiwanese children in their study and Franco et al included 63 Portuguese volunteers in their study.

These are applied at line 213-216.
10. Discussion, lines 155-156, “the report showed...between them”. Why there was no association between them?

**Answer:** However, they included only 50 French subjects in their study. In this large-scale study, there was no significant association between them. This difference could be related to the small sample size or could represent ethnic variations in biomechanical properties. These are applied at line 219-221.

11. Discussion, line 162, what is the authors’ view about this? Why there was no association?

**However, they included only 50 French subjects in their study. In this large-scale study, there was no significant association between them. This difference could be related to the small sample size or could represent ethnic variations in biomechanical properties. These are applied at line 228-230.**

12. Discussion, lines 180-184, Is this a speculation? Although CH and CRF correlate with CCT can they directly impact on IOP? How has mean CH and CRF been defined as the “specific values”? Is this through population studies, if yes this needs to be acknowledged with the relevant citation, if not it needs to be discussed accordingly. It is confusing what the authors are trying to say.

**Answer:** That is a speculation.

**As a next study, we are trying to find out the explicit equation of IOPcc using data from other patients. Because ORA actually measures only P1 and P2, IOPcc can be expressed as a linear combination of P1 and P2 by linear regression analysis. Because P2-P1=CH and IOPg=(P1+P2)/2, we can express IOPcc as linear combination of CH and IOPg. As**
a preliminary result, IOPcc was expressed as following,
IOPcc=IOPg-1.13(CH-10.9 mmHg)

Therefore, if CH is larger than 10.9 mmHg, IOPcc< IOPg and the IOP measured by the
Goldmann tonometer is overestimated. If CH is smaller than 10.9 mmHg, IOPcc> IOPg
and the IOP measured by the Goldmann tonometer is underestimated. These may be
clinical implications of CH and CRF. Because CH had also high values with large
corneal volume, the IOP measured by the Goldmann tonometer may be overestimated
in large volume cornea.

These are applied at line 248-259.

13. Discussion, lines 191-194, how does the example of keratoconus fit into this
study? As an example of altered biomechanical properties? Expand or remove.
Answer: We removed the sentence as the reviewer’s recommendation.

14. Discussion, lines 195-197, “....for refractive surgery”. Add and cannot be
extrapolated to larger populations or something similar.
Answer:
This study was a large-scale study, but has a limitation. The patients included in this
study were not representative for normal Korean population. They are young patients
who visited the eye clinic for refractive surgery. This is a kind of selection bias. There is
another large-scale study about determinants of corneal biomechanical properties in an
adult Chinese population[11]. In their study, CH was negatively associated with corneal
radius of curvature and positively associated with CCT. The CRF showed a negative
association with corneal radius of curvature, and was positively associated with CCT.
These are consistent with our results.
15. Discussion, lines 195-197, further to identifying the limitation provide evidence to the reader on whether there are other large scale studies to compare findings from this study? Also acknowledge the statistical biases this limitation causes.

**Other large scale study**

Statistical bias: selection bias

**Answer:**

This study was a large-scale study, but has a limitation. The patients included in this study were not representative for normal Korean population. They are young patients who visited the eye clinic for refractive surgery. This is a kind of selection bias. There is another large-scale study about determinants of corneal biomechanical properties in an adult Chinese population[11]. In their study, CH was negatively associated with corneal radius of curvature and positively associated with CCT. The CRF showed a negative association with corneal radius of curvature, and was positively associated with CCT. These are consistent with our results.

16. Discussion, lines 201-203, the conclusion is confusing. The authors have not explained what CH and CRF “really represent” as they also state in their aims. Are they markers of geometric and biomechanical properties of the cornea?

**Expand.**

**Answer:** We changed the conclusion in the discussion.

**In summary, in this study, which included 958 eyes from 958 Koreans, through**
multivariate analysis, we showed the associations between the biomechanical properties and the anterior segment parameters representing the geometric dimensions. CH was shown to be positively associated with the central corneal thickness and corneal volume and negatively associated with mean radius of corneal curvature. The association between CH and the anterior chamber volume was not significant. CRF was shown to be positively associated with the central corneal thickness and negatively associated with mean radius of corneal curvature. The associations of CRF with the corneal volume or anterior chamber volume were not significant. And we believe that CH and CRF might be factors that cause the IOP measured by the Goldmann tonometer to be overestimated.

These are applied at line 275-284.

Discretionary revisions

3. Introduction, line 41 “However, as far as we know, there is no...” change to “however, to the best of our knowledge, there is no other study...” there are many similar points across the text which could improve.

Answer: We changed the sentence as the reviewer’s recommendation

These are applied at line 80-81.

1. Introduction, line 42, add “respectively” after anterior chamber volume.

Answer: We added “respectively” after anterior chamber volume.

These are applied at line 82.

2. Methods, line 84, “CH and CRF was made...” “ was generated”

Answer: We changed the “made” to “generated”
3. Discussion, line 149, valid point but needs improvement.

Answer: We add some sentences and citations to improve the sentences.

In other words, the steeper the cornea was, the larger the CH and CRF were. Results in studies in which dynamic contour tonometry was used have suggested that corneal curvature affects corneal rigidity, with steeper corneas being more rigid [17, 18]. The more rigid corneas showed higher CH and CRF values.

These are applied at line 206-209.

4. Discussion, general, add a suggestion for future studies.

Answer: We added a suggestion for future studies.

As a next study, we are trying to find out the explicit equation of IOPcc using data from other patients. Because ORA actually measures only P1 and P2, IOPcc can be expressed as a linear combination of P1 and P2 by linear regression analysis. Because P2-P1=CH and IOPg=(P1+P2)/2, we can express IOPcc as linear combination of CH and IOPg. As a preliminary result, IOPcc was expressed as following,

\[ IOP_{cc} = IOP_g - 1.13(CH - 10.9 \text{ mmHg}) \]

Therefore, if CH is larger than 10.9 mmHg, IOPcc<IOPg and the IOP measured by the Goldmann tonometer is overestimated. If CH is smaller than 10.9 mmHg, IOPcc> IOPg and the IOP measured by the Goldmann tonometer is underestimated. These may be clinical implications of CH and CRF. Because CH had also high values with large corneal volume, the IOP measured by the Goldmann tonometer may be overestimated in large volume cornea.

These are applied at line 248-259.
Reviewer's report

Title: Biomechanical properties of the cornea measured with an Ocular Response Analyzer and its association with anterior segment parameters including corneal volume and anterior chamber volume

Version: 1 Date: 10 February 2013
Reviewer: Dimitra Makrynioti

Reviewer's report:

Major Compulsory Revisions

1. Abstract is missing

Answer: We inserted abstract in the manuscript.

These are applied at line 20-46

2. In the Methods: exclusion criteria: What about Contact Lens use? How long were subjects without contact lenses before test performance? I think details on this are essential.

Answer: We added the exclusion criteria about contact lens use.

We excluded the subjects who use contact lens within two weeks.

These are applied at line 125

3. The aim of the study is clearly posed – I am not quite sure though that the answer is given clearly for the last phrase of the aim (lines 45-46: “and to determine what the CH and CRF really represent”). You could answer more clearly on this in your discussion or remove this phrase.

Answer: We removed the rather vague purpose as the reviewer’s recommendation.
Minor Essential Revision

1. In the Methods: (line 59): How was the study sample size determined? Was there any power analysis performed? Please report if so.

   Answer: Sample size of 958 eyes has power of the test larger than 85% in multivariate analysis with seven independent variables, small effect size, $f^2=0.02$ ($R^2=1.96\%$) and level of significance $0.025^{[16]}$

   These are applied at line 156-158.

2. In the Methods: (line 59): when/ during what period did these patients visited the Eye Clinic?

   Answer: We added the information about the period.

   A retrospective review of 1020 patients who visited the BGN Eye Clinic (Seoul, Korea) for refractive surgery from January to December in 2011 was done.

   These are applied at line 99.

3. In the Results: (line 101): why special mention on male? Please explain – or give details on male & female.

   Answer: We mentioned the male without any significant implication. We added details on male and female at result section.

   These are applied at line 160-161

4. In the Discussion: (line 144, line 153, line 156, line 162): I think it would be useful you to give possible explanations/theories on why do you think you found those results.

   Answer:
They included only 50 French subjects in their study[10]. In this large-scale study, there was no significant association between them. This difference could be related to the small sample size or could represent ethnic variations in biomechanical properties.

These are applied at line 219-221, 228-230.

This difference could be related to the small sample size in the previous studies or could represent ethnic variations in biomechanical properties. Chang et al included 63 Taiwanese children in their study[5] and Franco et al included 63 Portuguese volunteers in their study[6].

These are applied at line 213-216.

5. Clinical Significance/use useful to discuss.

Answer: We modified the discussion focusing at clinical significance.

These are applied at line 248-259.

6. If you rephrase your summary and especially lines 201-203 it may give better the conclusion of your work.

Answer: We rephrase the summary as following.

In summary, in this study, which included 958 eyes from 958 Koreans, through multivariate analysis, we showed the associations between the biomechanical properties and the anterior segment parameters representing the geometric dimensions. CH was shown to be positively associated with the central corneal thickness and corneal volume and negatively associated with mean radius of corneal curvature. The association
between CH and the anterior chamber volume was not significant. CRF was shown to be positively associated with the central corneal thickness and negatively associated with mean radius of corneal curvature. The associations of CRF with the corneal volume or anterior chamber volume were not significant. And we believe that CH and CRF might be factors that cause the IOP measured by the Goldmann tonometer to be overestimated.

These are applied at line 275-284.

7. Please note: line 146, line 148, line 180: put full stop (.) after reference (e.g. line 146: "viscoelastic materials [8]." rather than “viscoelastic materials.[8]” ).

Answer: We put full stop (.) after reference.