

Peer Review File

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Reviewer A

Although the work regarding an interesting subject and is well structured and written, speculative assumptions are made. In some parts of the discussion, the work is not supported by appropriate and substantial references.

lines 176-178: remove this phrase

Reply: We have removed this phrase according to your advice.

lines 189-192; how can you say that visual acuity can be an indicator of retinal vessel circulation change? Make references; the reference 21 is not appropriate.

Reply: Thanks so much for your review and thoughtful advices.

Because there are evidences that amblyopic eyes show lower vessel density. There was no amblyopic eye in our study, and accordingly no difference in vessel density was found. Visual acuity means corrected visual acuity, that's what the amblyopia means. Thus we got the hypothesis. The reference 21(now 32) probably can support our hypothesis from the retina structure. We also add a latest reference (REF#31), which conclude that vessel density was correlated with visual acuity, to support our hypothesis. We have reorganized the content to make our expression more clear.

Changes in the text (page9-10, line194-202): “Lonngi et al.(29) observed significantly decreased vessel density in patients with amblyopia. Demirayak et al.(30) also found lower vessel density in amblyopic eyes than fellow eyes. Amblyopia means different corrected visual acuity in paired eyes. That is the key point that distinguishes our study from the two references above, resulting to no difference in vessel density between the eyes. This result inspired the hypothesis that visual acuity can be an indicator of retinal vessel circulation change. Similar results was derived from Liu's study(31) that vessel density was a prominent factor affecting visual acuity. The potential mechanism may be that nerve fiber and ganglion cell layer receive blood from the superficial retinal vascular plexus and the degree of perfusion may impact visual performance.(32)

Lines 209-211; remove.

Reply: Thanks for your advice and this phrase was removed.

Reviewer B

Myopia is a global health problem that has recently undergone an unprecedented rise, particularly in the developing countries of East and Southeast Asia. In the manuscript “The role

of magnification correction in macular vessel density assessment: A contralateral eye study in anisometropia patients”, authors investigated the impact of magnification correction in macular vessel density using OCTA in patients with anisometropia.

(1) There was a similar report (BMC Ophthalmol. 2019 Aug 5;19(1):171) in the PubMed. What is the novel idea in the paper? Please elaborate in the introduction.

Reply: Thanks so much for your review and advice. Actually, we have cited this references (now REF#13). They compared vessel density between amblyopic and normal eyes using anisometropia patients. And the results was controversial to some previous studies. (REF#11-12). The contradictory results inspired us to analyze the potential reasons. Though we also used anisometric patients, the main topic is to investigate the magnification correction' s effects on the results. We also excluded the effect from amblyopia, making our results more objective. We added some elaboration in the introduction part.

Changes in the text (page3, line60-65): “t has been reported that the average retinal blood flow and vessel diameter were significantly decreased in highly myopic eyes compared to normal eyes.(11, 12) However, identical vessel density in anisometropia induced amblyopic eyes also has been observed.(13) These inconsistent results inspired us to search for the root cause. Besides the effect of amblyopia, the error originated from magnification correction might partly explain these varied results. Because the error caused by magnification correction could result in variation of -20% to +10% in vessel density values.(14)”

(2) The running title should be revised.

Reply: Thanks for your helpful advice. We have revised the running title as you advice. Please let me know if further optimization needed.

Changes in the text (page 1, line 3):“Macular vessel density in anisometropia patients”.

(3) There were several grammar errors in the text. Such as “Investigate the impact of magnification correction in macular vessel density using OCTA in patients with anisometropia.” in the abstract.

Reply: Thank you so much for your careful review. According to your suggestion, we have checked our manuscript several times and such grammar errors were revised.

Changes in the text (page 2, line 24-25): “Investigating the impact of magnification correction in macular vessel density using optical coherence tomography angiography (OCTA) in patients with anisometropia.”.

(4) What is the meaning of “OCTA” in the abstract?

Reply: Sorry for our miss in this abbreviation. We added the full name of OCTA in the abstract.

Changes in the text (page 2, line 25): optical coherence tomography angiography (OCTA).

(5) In the introduction, please enrich the progress of the treatment for myopia. Please supplement the introduction of OCTA in the introduction.

Reply: Thanks for your kind advice. The treatment of myopia includes refractive surgery and various lenses. Though the treatment is not the main topic of our study, we added some references about myopia treatment in introduction part as you suggested.

We also added some introduction of OCTA regarding its mechanism, advantage and application in the introduction section.

Changes in the text (page 3, line 49-51): Though there are several refractive surgeries to correct myopia.(3) Controlling myopia progression is always the paramount topic. Strategies such as spectacles, contact lenses, orthokeratology, and pharmaceutical treatment are applied worldwide.(4, 5):

(Page3, line 54-59): “Optical coherence tomography angiography (OCTA) enables 3D visualization of the microvasculature by performing repeated B-scans to detect motion contrast and visualize vasculature. Multiple repeated B-scans were compared pixel by pixel to detect signal changes which occur due to flowing erythrocyte.(7) OCTA has the advantage of depth resolution, high contrast, well-defined image and non-invasive fashion. Up to now, OCTA was applied in several ocular pathology diagnosis, such as uveitis, cornea vascularization and retinal disease. (8-10) ”.

(6) How to treat for anisometropia? Please supplement in the text.

Reply: Thanks for your advice. Nowadays, anisometropia is treated by restoring balanced ocular dominance. Generally, refractive surgeries and rigid gas permeable are commonly used. According to your advice, we added several references in introduction section to make the content more detailed.

Changes in the text (page 4, line 69-71):“The principle of treating anisometropia is to restore balanced sensory ocular dominance between paired eyes.(15) Effective strategies includes refractive surgery and rigid gas permeable.(16, 17)”

(7) In the paper, the case samples were too small. How to handle with the issue?

Reply: Thanks for your kind suggestions. Because our center and the company did not reach an agreement in the sale, the instrument was put in our center for several months. This study is performed during this period (2017.8 to 2017.12), and we tried our best to enroll as much patients as possible. We agree with you that more cases would contribute to more scientific literature. Relative small sample size was one of limitations. Nevertheless, our research still has many novelties and hopes to make up for the shortcomings of the small sample size. First of all, patients with anisometropia without amblyopia are relatively rare, and the measurement results are more objective in such patients. Secondly, we show the blood flow values with and without correction, which is valuable in clinical application of OCTA. The study you mentioned above (BMC Ophthalmol. 2019 Aug 5;19(1):171) enrolled 15 cases and got the similar conclusion as ours. Lei’s (JAMA Ophthalmol. 2017;135:1092-1098) study also enrolled 22 cases to prove OCTA’s repeatability and reproducibility.

Changes in the text (page 11, line 219-220): “One is the relatively small sample size, from which several cases were excluded due to unstable fixation or low signal strength.”

(8) How to measure vessel density? Please supplement in the methods.

Reply: Thanks, your advice is helpful in enriching our methods part. Firstly, we described the definition of vessel density (Vessel length density (VLD, defined as the total length of perfused vasculature per unit area in a region of measurement), perfusion density (PD, defined as the total area of perfused vasculature per unit in a region of measurement)). All scans were analyzed using en face OCTA images generated automatically by the OCTA software. VLD and PD were measured automatically by the software that quantified vessel density of a local region of tissue according to Early Treatment of Diabetic Retinopathy Study subfields. We added a related reference (REF#20) of OCTA measurement, and the attached Figure 1 may also help readers understand.

Changes in the text (page 5, line 100-106): “Vessel length density (VLD, defined as the total length of perfused vasculature per unit area in a region of measurement) and perfusion density (PD, defined as the total area of perfused vasculature per unit in a region of measurement) were assessed via the prototype algorithm provided by Zeiss Meditec. One standard 3 × 3 mm scanning pattern was used for all patients. In accordance with the Early Treatment of Diabetic Retinopathy Study, vessel density was quantified in a set of five regions (**Figure 1**), thereby automatically producing a mean value of the entire scan area.”

(9) In the paper, the figure 1-3 were missing.

Reply: Thanks. The figures were uploaded separately. In the reversion, we added figures in the text. Please let me know if further revisions needed.

Changes in the text (page 17-18): Figures were attached.