Clinical science

Comparison of anterior segment optical coherence tomography angiography systems for corneal vascularisation

Marcus Ang,[1,2,3] Kavya Devarajan,[2] Suchandrima Das,[2] Tisha Stanzel,[2] Anna Tan,[1,2] Michael Girard,[2,4] Leopold Schmetterer,[2,3,5,6,7] Jodhbir Mehta[1,2,3,5]

[1]Singapore National Eye Centre, Singapore
[2]Singapore Eye Research Institute, Singapore
[3]Ophthalmology and Visual Sciences, Duke–National University of Singapore, Singapore
[4]Department of Ophthalmology, National University of Singapore, Singapore
[5]Nanyang Technological University, Singapore
[6]Department of Clinical Pharmacology, Medical University of Vienna, Austria
[7]Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Austria

Correspondence to
Dr Marcus Ang, Singapore National Eye Centre, 11 Third Hospital Avenue, Singapore 168751, Singapore; marcus.ang@snec.com.sg

ABSTRACT

Aim To newly describe a spectral-domain (SD) optical coherence tomography angiography (OCTA) for the cornea and directly compare two OCTA system scans of the same eyes with corneal vascularisation.

Methods Cross-sectional, observational, comparative case series. We performed sequential OCTA scans (10 eyes of 10 subjects with corneal vascularisation,4 scans each eye) repeated using split-spectrum amplitude decorrelation algorithm angiography system (SSADA, AngioVue; Optovue Inc, USA) and SD OCTA (Angioscan; Nidek Co. Ltd, Japan) in the same region of interest. We analysed all scan images for repeatability, image quality and vessel density measurements and compared OCTA systems.

Results We obtained substantial interobserver repeatability in terms of image quality score ($\kappa=0.86$) for all 80 OCTA scans (median age 49 years, 50% women). The correlation was moderately good ($r=0.721$) when comparing vessel density measurements between OCTA systems, but greater in the SSADA compared with SD OCTA system (mean vessel density $20.3\pm4.9\%$ vs $15.1\pm4.2\%$, respectively; $p<0.001$).

Conclusion In this pilot clinical study, we describe successful delineation of corneal vessels with substantial image quality using a new SD OCTA system. The vessel density measurements were greater using the SSADA compared with SD OCTA system in the same area of corneal vascularisation. Further studies are required to confirm the advantages, limitations and differences between these OCTA systems for the anterior segment.

CrossMark

INTRODUCTION

Anterior segment angiography has a wide variety of clinical applications, ranging from the diagnosis of corneoscleral inflammatory disorders to optimising the treatment, such as anti-vascular endothelial growth factor therapy or fine-needle diathermy for corneal vascularisation.[1] Diagnostic techniques such as indocyanine green angiography (ICGA) have been described for the anterior segment, but these are invasive and exposes patients to potentially serious adverse reactions.[2] Therefore, as new antiangiogenic treatments emerge for the cornea and anterior segment, it has been recognised that new imaging techniques for measuring changes in corneal vascularisation are becoming an important aspect for research and development.[3]

Recently, non-contact optical coherence tomography angiography (OCTA) has been described

to delineate vessels in the cornea and anterior segment.[4] These optical coherence tomography (OCT) imaging systems either detect change in phase, amplitude or the full OCT signal in order to identify blood flow through vessels.[5] As current OCTA systems are optimised for the retina, we had previously described a technique adapted to perform scans in the anterior segment for normal corneal and limbal vessels.[6] With these newly developed imaging systems, we are now able to evaluate corneal pathologies and their associated vessels in a rapid, non-invasive manner.[6] However, while studies are emerging that suggest OCTA imaging may delineate both normal and abnormal anterior segment vasculature with substantial consistency, its role in clinical evaluation of patients has not been fully established.[7]

The split-spectrum amplitude-decorrelation angiography (SSADA) from AngioVue (Optovue Inc, USA) has been shown to improve the signal-to-noise ratio of flow detection, which has been useful for visualising various vasculature networks within the eye.[7] More recently, other systems such as a swept source OCTA system (Deep Range Imaging, Topcon, Japan) have been shown to be promising in terms of visualising anterior segment vasculature; however, the images are very different from the SSADA system in terms of size and image resolution.[8] Previously, there have been no direct comparative studies to examine different OCTA imaging in the same eyes of the same cohort of patients. Therefore, we conducted this pilot clinical study to evaluate a new corneal module from a spectral-domain (SD) OCTA system (Angioscan, Nidek Co Ltd, Japan) not formerly used for the anterior segment and compared this to a previously described SSADA OCTA system, in the same eyes of the same patients with corneal vascularisation.

METHODS

We prospectively recruited subjects with corneal vascularisation at Singapore National Eye Centre from January to July 2016. We included patients with superficial and deep corneal vascularisation secondary to ocular surface diseases extending >1 mm from the limbus into the cornea, while eyes with active inflammation, infection or ulceration were excluded to prevent imaging artefacts and obscuration of corneal vessels. Our study followed the principles of the Declaration of Helsinki, with ethics approval obtained from our local

Institutional Review Board and informed consent was obtained from all patients.

Angiography technique

All OCTA scans of these areas were performed using (a) a SSADA system (AngioVue, Optovue Inc, USA) and (b) a SD OCTA system (Angioscan, Nidek Co Ltd, Japan) in the same region of interest (ROI) of all eyes in the same patient, sequentially in random order on the same day. Each scan was taken four times in the same quadrant (each requiring average 4–6 s) using both systems, ensuring a good signal strength using previously described techniques.[6] Essentially, all eyes had 6×6 mm scans of the identified area of corneal vascularisation, using the AngioVue OCTA system (Optovue Inc Fremont, California, USA) with the long corneal adaptor module. In the SSADA OCTA system used for this study, the autofocus function had to be deactivated, and the lens moved very close to the corneal surface before fine-tuning and manual adjustments to the focal lengths made to achieve adequate focus on the area of interest in the cornea. Scans had transverse resolution of 15 µm and axial resolution of 3 µm using a light source centred on 840 nm with a beam width of 22 µm. Coronal or 'en face' OCTA scan images were reconstructed from 304×304 A scans captured at 70 000 scans/s.[9] For the SD OCTA system (Angioscan), a similar technique as above was used to obtain 6×6 mm scans with a lateral resolution of 20 µm and axial resolution of 7 µm using a light source centred on 880 nm. Scan images were reconstructed from 256×256 A scans captured at 53 000 scans/s. Signal strength indices were obtained from each system, which are derived and reported independently as scores proprietary to the technology. Thus, adjustments and calculations were made to compare both system based on scores out of 4 and 10 for an average intersystem comparison. Technical details of each system are outlined in table 1.

Image analysis

Image analysis was performed using a previous described technique.[2] Essentially, all OCTA images were exported from the system in standard image segmentation measurements, that is, 300 µm below the epithelium, as a portable network graphics image file into the National Institutes of Health Image J V.1.38x (NIH, Bethesda, Maryland, USA) software for analysis using a previously described method.[6] Briefly, the 'adjust threshold' function set to 'default' to reduce the surrounding noise and highlight the blood vessels by a single analyst, masked to the diagnosis and slit-lamp photographs.[10] The ROI was identified from the marginal corneal vascular arcade, in the corresponding area of the corneal vascularisation of all OCTA images. Next, we used a selective filter to produce the vessels as a binary image, with pixel resolution used to determine percentage of vessels highlighted from the ROI to determine vessel density on OCTA scans as previously described.[11] We assessed the image quality score using a recognised system, that is, 0–4 (0, no vessel discernible; 1, poor vessel delineation; 2, good vessel delineation; 3, very good vessel delineation; 4, excellent vessel delineation) performed by two independent masked assessors.[12] We also documented the signal strength of all OCTA scans as determined by each system and compared each image from the same ROI comparing both systems.

Statistical analysis

We analysed all scan images obtained for repeatability, image quality and vessel density measurements between angiography techniques. The measurements of vessel density from the SSADA and SD OCTA systems were analysed and mean difference in vessel density measurements between the two machines were then assessed using Mann-Whitney test. Median differences for image scores were assessed using non-parametric Wilcoxon signed rank test, where appropriate. Statistical analysis was performed using Statistical Programme for Social Sciences V.20.0 for Windows© (2011 SPSS©, IBM Corp, USA). We calculated the Pearson correlation (r) between OCTA systems and kappa coefficient (κ) value for the interobserver agreement of scans using the image quality score, where κ ≤0.2 was considered slight, 0.21–0.40 weak, 0.41–0.6 moderate, 0.61–0.8 substantial and

Table 1 Comparison of OCTA systems for anterior segment imaging

	AngioVue RTVue XR Avanti	Angioscan RS-3000 Advance	Triton prototype* DRI-OCT (swept source)
Imaging company	Optovue, Fremont, California, USA	Nidek, Gamagori, Aichi, Japan	Topcon Corporation, Tokyo, Japan
Scanning speed	70 000 scans/s	53 000 scans/s	100 000 scans/s
Scanning volume	304×304 A scans	256×256 A scans	320×320, 512×512 A scans
Algorithm	SSADA	Complex difference (full spectrum amplitude)	OCTA-ratio analysis (full spectrum amplitude)
Type of algorithm	Amplitude	Amplitude+phase	Amplitude
Scan area (macula)	3×3, 6×6, 8×8 mm	3×3 to 9×9 mm (12×9 panorama)	3×3, 4.5×4.5 mm 6×6, 9×9 mm
Optical resolution (axial)	3 µm	7 µm	8 µm
Optical resolution (lateral)	15 µm	20 µm	20 µm
Light source	840 nm	880 nm	1050 nm
Axial imaging depth	2–3 mm	2.1 mm	2.6 mm
Cross-sectional OCTA	Yes	No	Yes
Motion correction	Yes	No	No
Projection artefact removal	Yes	Yes	Yes
Anterior segment function	Yes	No (prototype)	No
Quantitative analysis	Yes	Yes	Yes (prototype)
Comparative follow-up	Yes	No	Yes

*Prototype: not used in this study, but placed in table for comparison, as this is not commercially available for anterior segment imaging.[8]
OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; SSADA, split-spectrum amplitude-decorrelation angiography.

0.81–1.0 considered 'almost perfect' in agreement.[13] A p value <0.05 was considered statistically significant.

RESULTS

In this cross-sectional clinical study, we analysed 80 scan images (40 from each OCTA system) from 10 eyes of 10 patients with corneal vascularisation. The median age of patients was 49 (23-73) years, 50% women. All eyes had significant superficial corneal vascularisation from early limbal stem cell deficiency (mean duration of follow-up 12 ± 3 months) from ocular surface disease, extending >1 mm from the limbus, with median best-corrected visual acuity of 20/40 (20/30–20/80). All patients did not have active inflammation, corneal infiltrates or melts in association with the corneal vascularisation.

Image quality

There was substantial interobserver repeatability in terms of image quality score ($\kappa=0.86$) for all OCTA scans on both systems (type of OCTA systems were masked to the observers). The overall median image quality index for SSADA OCTA system (2.0, 2.0–4.0) was comparable to that for the SD OCTA (2.0, 2.0–3.0) system (p=0.08). There was no statistical difference between the median repeatability scores of the SD OCTA and the SSADA systems (5.0, 3–5 vs 4.5, 4–5; p=0.057).

Signal strength

As signal strength indices were derived from each system independently, scores were averaged to allow for comparisons to be made between systems. The medians of the SD OCTA and SSADA OCTA systems for signal strength index were also reported to be significantly different for both scales (out of 10) (SD OCTA (9.2, 7–10); SSADA OCTA (5.1, 3–8), p=0.004) and (out of 4) (SD OCTA (3.6, 3–4), SSADA OCTA (2.6, 1–3), p<0.001).

Vessel density

The correlation between the two OCTA systems was moderately good in terms of vessel density (r=0.721). However, the mean vessel density measured by SSADA OCTA system was significantly greater than that measured by SD OCTA system (20.3%±4.9% vs 15.1%±4.2%, respectively; p<0.001) (figure 1).
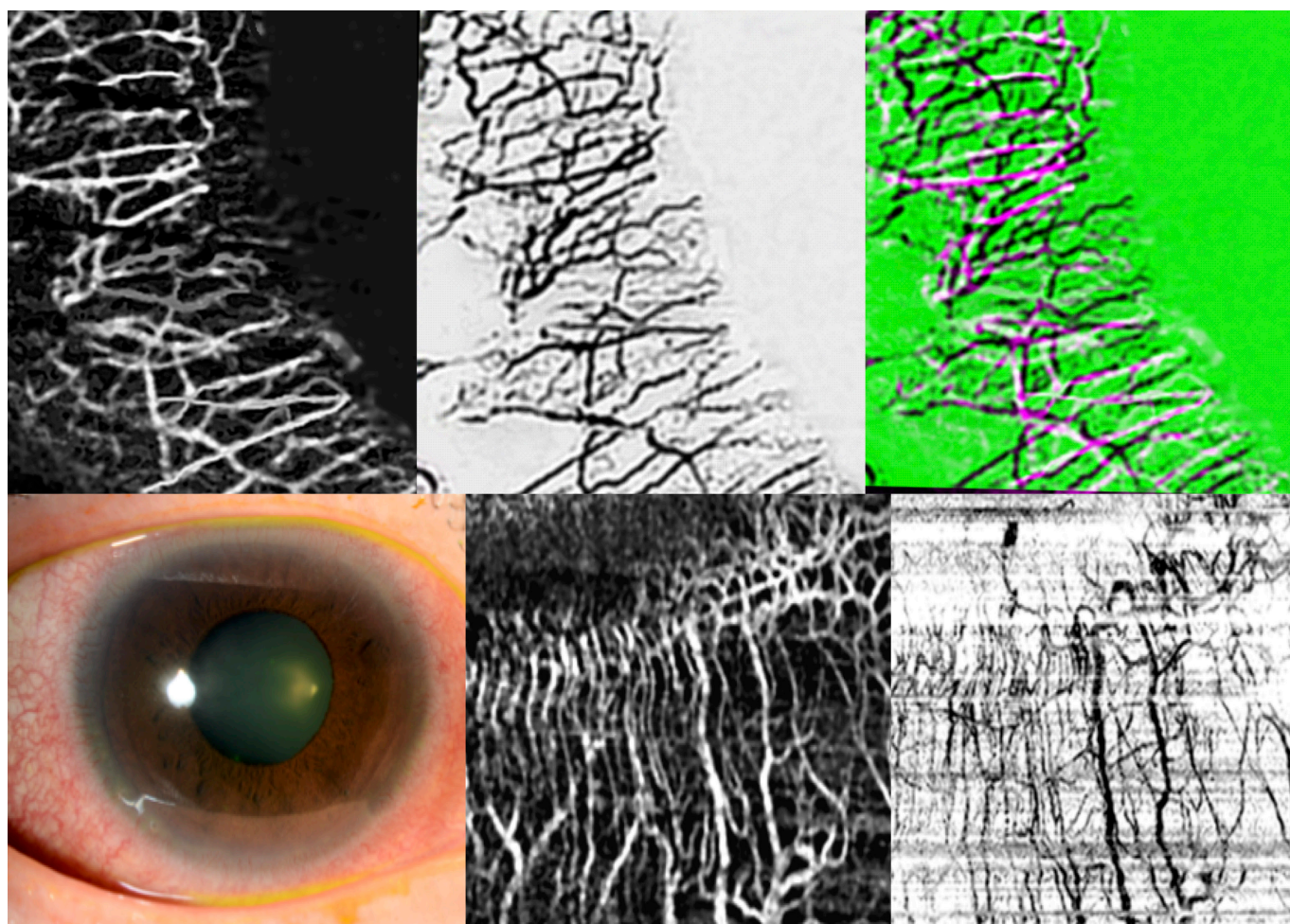

Figure 1 Examples of image analysis comparing SSADA system SD OCTA systems. (Top) SSADA OCTA (left) compared with SD OCTA (centre) scans of the inferior temporal quadrant of eye with early limbal stem cell deficiency, disruption of the limbal vascular arcades and corneal vascularisation (segmentation 0–300 µm from epithelium). The overlaid processed images were analysed (top right) to compare vessel density measurements. (Bottom) slit-lamp photo of the same eye (left) to demonstrate the difference between temporal and inferior quadrant scans. Higher resolution of SSADA OCTA (centre) compared with SD OCTA (right) scans of the inferior aspect of eye with corneal vascularisation demonstrating the limbal vascular arcades in greater detail (segmentation 0–300 µm from epithelium). With increased resolution, images contain more motion artefacts, which may be removed using image processing. OCTA, optical coherence tomography angiography; SD, spectral-domain; SSADA, split-spectrum amplitude decorrelation angiography.

DISCUSSION

In this pilot study, we describe a new anterior segment module on the SD OCTA system and objectively compare this with the SSADA OCTA system in the same eyes to study the advantages and limitations of each OCTA system. Our preliminary clinical study comparing these two relatively new OCTA imaging systems for the cornea suggests that the images of corneal vascularisation may be obtained with good vessel delineation ('good' vessel delineation in both systems, p=0.08). However, we also observed that the SSADA OCTA system detected a greater vessel density compared with the SD OCTA system in the same quadrant of the same eye with corneal vascularisation (20.3%±4.9% vs 15.1±4.2%, respectively; p<0.001). The observed difference of corneal vessel density measured by the two systems in our study is probably of minimal clinical relevance, but should be taken into consideration in future studies planning to use different OCTA systems to monitor treatment outcomes. These observations may be due to fundamental differences in the imaging algorithms or disparities that may have arisen from the image produced itself, which may have been affected by factors such as non-parallel segmentation or projection artefacts.[5] Moreover, the two systems have different A-scan rates as well as different scanning volumes, and therefore are sensitive to different velocity ranges. However, the aim of this pilot clinical study was not to determine whether either imaging technique was superior or why these observed differences exist but instead to demonstrate the usefulness of this fairly unproven OCTA retinal imaging system adapted for the cornea and how the measurements compare among each system when used in a clinical setting.

This study also reinforced several advantages, as well as the current limitations, of OCTA adapted for the anterior segment and cornea. The first and most obvious advantage of the OCTA is its ability to perform non-contact, cross-sectional and coronal sections of areas of interest in the cornea and associated vessels within seconds. The SSADA OCTA system requires two scans to be taken separately each taking 3–4 s, and thus any eye movement may produce motion artefacts. However, the SSADA OCTA system has inbuilt motion correction software to compensate for these saccadic movements.[14] On the other hand, the SD OCTA system takes 5–6 s for one full scan, which could potentially actually lead to more motion artefacts in patients who cannot fixate due to poor vision. Although we found that SD OCTA was able to scan images with greater signal strength index, these values are calculated internally and independently by each system and thus, may not be directly comparable. Nonetheless, both systems produced OCTA scans with good signal strength and interobserver repeatability in terms of image quality (κ=0.86).

The second major difference between the systems is that the field of view for the SD OCTA system is slightly larger (9×9 mm and 12×9 mm with panorama setting) compared with the SSADA OCTA system (8×8 mm). This may be advantageous in the cornea and anterior segment, as large areas of cornea vascularisation often extend across quadrants and larger scan areas may reduce the number of scans required. Moreover, the SD OCTA system currently has montage software that splices together adjacent OCTA images—although designed only for the retina, it may be extended to the anterior segment in future. Both systems should see improvements to the software or optimisation for the anterior segment to introduce an eye tracker or iris registration for the anterior segment, which may further improve the field of view and image resolution.[15] The third difference is that the SSADA OCTA system allows for consecutive OCTA scans to be viewed while adjusting the segmentation simultaneously, which is good for progression assessment. This could be a useful addition to other OCTA systems to allow for landmark registration on the anterior segment and progression analysis in future developments.[7]

Lastly, our study revealed the clinical logistics involved with performing the OCTA and introducing two different systems into the clinic. As all scans were performed by trained technicians, most reported a relatively easy learning curve with both OCTA systems, as they are similar to already existing OCT models. As this is a non-invasive procedure that requires a few minutes to perform multiple scans with sufficient consistency, patients were willing to have repeated images taken, rather than being exposed to the potential adverse reactions associated with the administration of intravenous dyes. Also, significant time, preparation and safety precautions are required before each ICGA imaging session; and some patients may not be suitable for this procedure at all due to various contraindications.[16] However, it must be emphasised that current OCTA systems are not optimised for the anterior segment, with an inability to differentiate between arteries and veins, while adjustments had to be made to the scanning technique while using the lens adapter. Moreover, the interpretation of OCTA images require careful examination for artefacts such as any hyper-reflective structures, for example, from corneal fibrosis or scarring.[17] These can be detected on the corresponding structural OCT, which can sometimes cause falsely bright images on the OCTA even in areas devoid of flow and should be interpreted by the clinician examining the OCTA images.

The potential clinical applications of OCTA for the anterior segment, apart from those already mentioned, could also extend to assessment of corneal inflammation or infections, corneal graft vascularisation and even effects of the episcleral venous plexus on raised intraocular pressure.[18] Moreover, the combination of information from the cornea and anterior segment OCT scans,[19] with the corresponding angiography images could bring additional information when making clinical decisions such as planning corneal transplantation in complex eyes.[20] We recognise the limitations of this pilot study, which describes the adaptation of commercial OCTA systems for the anterior segment in a small number of eyes. Ideally, a large prospective study with comparisons to slit-lamp photography and invasive angiography should be performed to evaluate both OCTA systems. However, we had previously described the comparison of OCTA to ICGA and both techniques were found to be relatively comparable.[2]

In conclusion, we describe a new rapid, non-contact SD OCTA system that can successfully delineate vessels in the anterior segment with good repeatability. While there was moderate correlation between two OCTA systems, the vessel density measurements using the SSADA OCTA system was found to be significantly greater than that measured with the SD OCTA system. Further prospective studies are required to confirm if these new imaging technique may be used for vessel quantification and serial imaging.

Ethics approval SingHealth Institutional Ethics Review Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Any unpublished data may be obtained from the corresponding author.

REFERENCES

1 Spiteri N, Romano V, Zheng Y, *et al*. Corneal angiography for guiding and evaluating fine-needle diathermy treatment of corneal neovascularization. *Ophthalmology* 2015;122:1079–84.

2 Ang M, Cai Y, MacPhee B, *et al*. Optical coherence tomography angiography and indocyanine green angiography for corneal vascularisation. *Br J Ophthalmol* 2016;100:1557–63.

3 Cursiefen C, Colin J, Dana R, *et al*. Consensus statement on indications for anti-angiogenic therapy in the management of corneal diseases associated with neovascularisation: outcome of an expert roundtable. *Br J Ophthalmol* 2012;96:3–9.

4 Ang M, Sim DA, Keane PA, *et al*. Optical Coherence Tomography Angiography for Anterior Segment Vasculature Imaging. *Ophthalmology* 2015;122:1740–7.

5 Jia Y, Tan O, Tokayer J, *et al*. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express* 2012;20:4710–25.

6 Ang M, Cai Y, Shahipasand S, *et al*. En face optical coherence tomography angiography for corneal neovascularisation. *Br J Ophthalmol* 2016;100:616–21.

7 Cai Y, Alio Del Barrio JL, Wilkins MR, *et al*. Serial optical coherence tomography angiography for corneal vascularization. *Graefes Arch Clin Exp Ophthalmol* 2017;255:135–9.

8 Ang M, Cai Y, Tan AC. Swept Source Optical Coherence Tomography Angiography for Contact Lens-Related Corneal Vascularization. *J Ophthalmol* 2016;2016:1–3.

9 Spaide RF, Klancnik JM, Cooney MJ. Retinal vascular layers in macular telangiectasia type 2 imaged by optical coherence tomographic angiography. *JAMA Ophthalmol* 2015;133:66–73.

10 Sharma A, Bettis DI, Cowden JW, *et al*. Localization of angiotensin converting enzyme in rabbit cornea and its role in controlling corneal angiogenesis in vivo. *Mol Vis* 2010;16:720–8.

11 Zheng Y, Kaye AE, Boker A, *et al*. Marginal corneal vascular arcades. *Invest Ophthalmol Vis Sci* 2013;54:7470–7.

12 Anijeet DR, Zheng Y, Tey A, *et al*. Imaging and evaluation of corneal vascularization using fluorescein and indocyanine green angiography. *Invest Ophthalmol Vis Sci* 2012;53:650–8.

13 Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159–74.

14 Sharma S, Ang M, Najjar RP, *et al*. Optical coherence tomography angiography in acute non-arteritic anterior ischaemic optic neuropathy. *Br J Ophthalmol* 2017;101:1045–51.

15 Girard MJ, Ang M, Chung CW, *et al*. Enhancement of corneal visibility in optical coherence tomography images using corneal adaptive compensation. *Transl Vis Sci Technol* 2015;4:3.

16 Kwiterovich KA, Maguire MG, Murphy RP, *et al*. Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. *Ophthalmology* 1991;98:1139–42.

17 Chung CW, Ang M, Farook M, *et al*. Enhancement of Corneal Visibility in Optical Coherence Tomography Images with Corneal Opacification. *Transl Vis Sci Technol* 2016;5:3.

18 Ang M, Sng C, Milea D. Optical coherence tomography angiography in dural carotid-cavernous sinus fistula. *BMC Ophthalmol* 2016;16:93.

19 Ang M, Chong W, Tay WT, *et al*. Anterior segment optical coherence tomography study of the cornea and anterior segment in adult ethnic South Asian Indian eyes. *Invest Ophthalmol Vis Sci* 2012;53:120–5.

20 Ang M, Mehta JS, Sng CC, *et al*. Indications, outcomes, and risk factors for failure in tectonic keratoplasty. *Ophthalmology* 2012;119:1311–9.

BJO

Comparison of anterior segment optical coherence tomography angiography systems for corneal vascularisation

Marcus Ang, Kavya Devarajan, Suchandrima Das, Tisha Stanzel, Anna Tan, Michael Girard, Leopold Schmetterer and Jodhbir Mehta

---

Updated information and services can be found at:

http://bjo.bmj.com/content/early/2018/01/03/bjophthalmol-2017-311072

These include:

References	This article cites 20 articles, 7 of which you can access for free at: **http://bjo.bmj.com/content/early/2018/01/03/bjophthalmol-2017-311072#ref-list-1**
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes