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The Impact of Deterministic Signal Loss on OCT Angiography Measurements

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Purpose: In this study, we aimed at investigating the impact of deterministic signal loss on image quality and, thus, on optical coherence tomography angiography (OCTA) measurements performed by the RTVue-XR Avanti System.

Methods: Absorptive filters with different optical densities (ODs) were used to simulate signal loss in a controlled way in 30 eyes from 15 healthy subjects. Scan Quality (SQ), provided by the AngioVue software, was applied as a measure of image quality.

Results: Assessing the effect of decreased light transmittance on SQ values as well as that of attenuated image quality on OCTA parameters revealed a strong systematic dependence between these quantities. Attenuated image quality was associated with significantly decreased macular and peripapillary vessel density (VD) values, and we calculated a correction factor of 2.27% to 3.97% for a one-unit change in SQ for the different VD parameters.

Conclusions: Our findings suggest that the influence of systematic changes in image quality on OCTA parameters needs to be considered during patient follow-up in order to make valid assessment of progression.

Translational Relevance: For accurate evaluation of longitudinal changes in OCTA parameters, equal scan quality or using a correction factor is suggested.

Introduction

Optical coherence tomography angiography (OCTA) is an emerging noninvasive imaging technique that is separately able to visualize the various retinal and choroidal capillary layers without the need for intravenous dye injections. OCTA provides both structural and blood flow information of the retina, which enables us to delineate the retinal vasculature in fine detail, allowing better visualisation of the microvascular abnormalities and capillary dropout areas in retinal vascular diseases. Owing to the short acquisition time and because it is noninvasive, OCTA is beneficial to patient comfort and can be repeated at any time during follow-up visits. Numerous studies have described the high accuracy and reproducibility of OCTA parameters in normal subjects,[1–8] as well as in patients with diabetes,[9] glaucoma,[6] ischemic optic neuropathy,[10] and retinal vascular diseases.[4,11,12] Longitudinal monitoring of OCTA parameters might play a significant role in follow-up on different diseases, such as diabetic retinopathy, glaucoma, and according to recent studies, also in dementia.[13,14] Although it is known that the quality of the OCTAs is critical for accurate medical diagnosis, the effect of image quality on quantitative OCTA parameters has not yet been completely explored. A recent study evaluated the relationship between Signal Strength Index (SSI) and macular superficial vessel density (SVD) measurements on two OCTA systems, in which signal strength reduction was generated by either neutral density filters or defocus.[15] Nevertheless, neither the effect of image quality on further OCTA parameters, nor a correction factor for image comparisons has been determined in their study. It is already understood that OCTA image quality varies greatly and depends on a

number of factors, including media opacities, saccadic eye motion, blink artifacts, double vessel artifacts, patient cooperation, and OCT operator skills.[16,17] In previous studies, media opacities were confirmed to be a reason for signal loss,[18] and lower image quality was associated with an increase in artifact frequency and with lower measurement repeatability in healthy volunteers.[19] One previous study demonstrated that cataracts can significantly influence quantitative vasculature measurements, even in high-quality images using swept-source OCTA.[20] Another recent study described that posterior subcapsular cataract can induce reduction in peripapillary VD that may falsely suggest glaucoma progression.[21] It has also been shown that images with lower signal-to-noise ratio are associated with less accurate segmentation of retinal layers and erroneously lower the results of thickness measurements.[22–25] Although these previous studies reported the repeatability of OCTA measurements from scans with different image quality (i.e. the statistical error), there is a lack of data on the deterministic connection between image quality and OCTA parameters (i.e. the systematic error). Inaccuracies in these measurements could have important consequences, as clinicians might misinterpret a change in an OCTA parameter due to loss of signal intensity as a true change on a follow-up scan. This should especially be taken into consideration in the monitoring and management of diseases with slow progression, such as patients with glaucoma.

The image quality of OCT scans is characterized by various indicators calculated directly from the raw optical signal (interferogram) acquired by the device. There are also diverse acceptance ranges and thresholds recommended by OCT manufacturers for their different commercially available devices.[26] SSI and Scan Quality (SQ) index are automated quality indices produced by the phase 6.5 and phase 7.0 versions of the RTVue-XR AngioVue software, respectively. With respect to the current study, the AngioVue software (version 2017.1, phase 7 update) supplied with the RTVue-XR Avanti System provides the SQ index as a measure of image quality. Although its precise formulation is not disclosed, the unitless SQ offers an objective scalar parameter in the range of 0 to 10 (the larger the better), taking into consideration errors coming from eye motion, defocus, and signal-to-noise ratio. This latter is affected by the intensity of the reflected light during scanning as well as optical/electronic noise factors. The recommended cutoff for acceptable image quality for the AngioVue system is an SQ score of 6 and above.

In this study, we investigate the influence of deterministic signal loss on OCTA image quality and OCTA measurements performed by the RTVue-XR Avanti System. Our final goal was to determine the relationship between the SQ index and measured angiographic parameters, as well as to provide a correction factor that can be used to compensate for changes in the value of SQ during patient follow-up.

Methods

A total of 30 eyes from 15 healthy subjects (6 men and 9 women, mean age: 34.33 ± 13.22 years) from the outpatient clinic of the Department of Ophthalmology at Semmelweis University were involved in this prospective, observational, cross-sectional study. The study was conducted according to the Declaration of Helsinki, with respect to relevant national and local requirements, and was approved by the National Drug Agency's Ethical Review Board for Human Research. All subjects gave their written informed consent. Ocular health was confirmed by undertaking a comprehensive ocular examination of each subject. Optical coherence tomographic angiography imaging was performed using the AngioVue OCTA system with an split-spectrum amplitude decorrelation angiography (SSADA) software algorithm. The AngioAnalytics software of the AngioVue system—which has an automated segmentation algorithm—was used to assess superficial vessel density (SVD) and deep vessel density (DVD) in the central 3 × 3 mm macular and in the 4.5 × 4.5 mm peripapillary region. In addition, the size of the foveal avascular zone (FAZ) and non-flow (NF) area at the level of the superficial capillary plexus were evaluated by the software, alongside the central retinal thickness (CRT) and peripapillary retinal nerve fiber layer (RNFL) thickness being measured. In the course of image selection, segmentation errors were meticulously checked on each B-scan. As a result, solely those OCTAs with an accurate segmentation at the level of the superficial and deep vascular plexus were selected for further analysis. The criteria used to identify poor quality scans and exclude them from the study included the following: autosegmentation alignment errors at the level of the retinal plexuses, images with artifacts such as the double vessel pattern—in which two copies of each blood vessel appears connected to software correction of ocular motion—significant dark areas from blinks, white line artifacts and vessel discontinuities induced by microsaccades, as well as shadowing artifacts and projection artifacts. As a result, no segmentation line required manual modification during image analysis and all analyzed scans were free of projection artifacts.

Table 1. Average Change in OCTA Scan Quality Due to Signal Loss by Placing Absorptive Filters with Decreasing Optical Transmittance in front of The Eye During The Measurement

	Optical Quality			Change in Scan Quality			
	Optical Density	Light Transmittance	Filter Thickness	Mean	SE	95% CI	*P* Value
No filter	0 ($n = 60$)	100%	–	–	–	–	–
Glass plate	0.04 ($n = 30$)	91.7%	2.0 mm	−0.10	0.07	−0.28 to 0.08	0.17
Absorptive filter*	0.09 ($n = 30$)	81.9%	0.76 mm	−0.57	0.15	−0.18 to −0.96	<0.001
	0.13 ($n = 30$)	74.9%	1.20 mm	−1.00	0.20	−0.49 to −1.55	<0.001
	0.25 ($n = 30$)	56.6%	2.90 mm	−1.33	0.12	−1.02 to −1.64	<0.001
	0.36 ($n = 30$)	43.8%	2.50 mm	−1.71	0.14	−1.35 to −2.07	<0.001

Note: *P* values were calculated for comparisons to SQ from baseline scans obtained without using absorptive filter (reference measurement). Bonferroni correction was used to adjust confidence intervals for multiple comparisons.

*Uncoated absorptive neutral density filter, Edmund Optics Ltd., Barrington, NJ, USA.

Measurements in Healthy Subjects Using Absorptive Filters

In OCT, the eye is illuminated using the partially coherent (i.e. quasi-monochromatic) light of a superluminescent diode, having its energy focused into a small spot on the retina.[27] Certain diseases, like cataract, reduce the amount of light power reflected back into the equipment, causing a deterministic drop of signal-to-noise ratio in the recorded interferograms (i.e. A-scans). We used absorptive neutral density filters to simulate this signal loss, hence OCT image degradation, in a controlled way. Although other filters, such as scattering and defocus filters, could also be considered to affect measurement values, the attenuation of scan quality using absorption filters is a proven way to mimic image degradation observed in a clinical practice.[26] The light attenuation of an optical filter can be expressed by providing its optical density (OD), which depends on the wavelenght (λ). The fraction of light power that passes through the filter is the transmittance (T), and OD is defined as $OD = -\log(T)$. An OD of 0.3, for example, corresponds to a T of 0.5 (T% = 50%). The central wavelength of the OCT light source is $\lambda = 840$ nm, the typical spectral width of such a superluminescent diode is approximately 40 nm. Correspondingly, our filters (uncoated absorptive neutral density filter, Edmund Optics Ltd., Barrington, NJ, USA) were measured in the 820 to 860 nm wavelength range by a Perkin-Elmer Lambda 35 spectrophotometer, the obtained average T and OD values are listed in Table 1. OCTAs of the 3 × 3 mm macular and 4.5 × 4.5 mm peripapillary area were acquired under standardized dim light conditions, as a result, a decrease in scan quality due to alterations in pupil size was not relevant during consecutive image acquisition. Scans were taken in a random order both with and without the absorptive filter being placed in between the equipment and the eye, at approximately 10 mm from the eye. All subjects underwent two image acqusitions (one macular and one optic disc scan) without the absorptive filter and with two randomly selected absorptive filters in a random order. When using the filters, we applied an approximately 10-degree tilted position in order to avoid false reflection from them back into the instrument. All measurements were taken by the same experienced examiner. The SQ value of each scan provided by the AngioVue software was collected to quantify the OCTA image quality. Only those images with an SQ score of at least 5 were included in the statistical analyses.

Regarding the usage of absorptive filters, we must make a remark. Such optical elements are manufactured in the form of glass plates, having a finite thickness of 0.76 to 2.90 mm (Table 1). Inserting one such plate in the light path will somewhat increase the optical path length the same way as if the elongated eye of a strongly myopic patient is measured. OCT scans are sensitive for such changes (i.e. the image quality drops when not used in optimum circumstances). Because the OCT manufacturer has not disclosed any details about how the different lengths of individual eyes are treated by their equipment, we are not able to separate image degradation resulting from absorption or optical path length increase. Instead, we quantify the signal loss introduced by a given filter by one single number SQ including both effects. In order to rule out the effect of increased optical path length on image degradation, scans were also taken by placing a clear piece of glass (Schott B270 glass) of 2-mm thickness—which is close

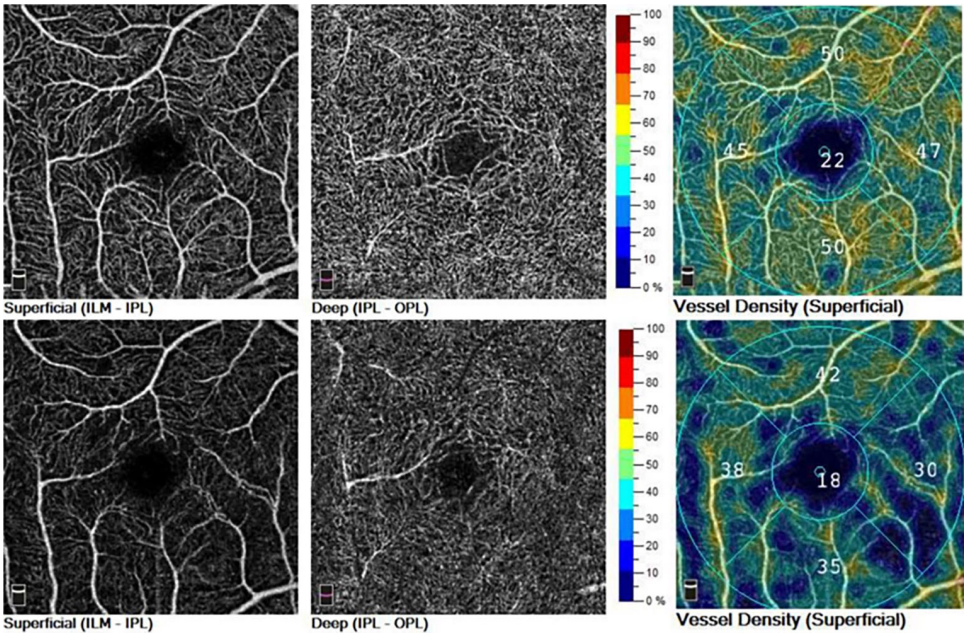

Figure 1. En face OCTA imaging of the superficial and deep retinal capillary plexus (SCP and DCP) as well as SCP VD (SQ = 9, top row) and by decreasing light transmittance by using an absorptive optical filter OD 0.25 (SQ = 6, bottom row) in the same healthy subject. In addition to the general reduction in the visibility of the retinal microvasculature in scans with lower image quality, focal areas of vascular attenuation and significant reduction in SCP VD are visible.

to that of the absorptive filters—in between the equipment and the eye and SQ values were compared to those without glass plates.

Statistical Analysis

A priori sample size calculation (power = 0.90; P = 0.05, clinically important difference in SQ: 1) for one-sample t-test was performed, as it was considered the most suitable built-in option for power calculation for the current study in our software package.[28] This sample calculation determined that the minimum number of eyes to include has to be 20 eyes of 10 subjects. In order to provide reliable statistical results, 30 eyes of 15 subjects were analyzed ultimately in this study. The correlation between the SQ values and the OD of the filters—as well as the effect of attenuated image quality on OCTA parameters—was assessed using multivariable regression on repeated measures via generalized estimating equation (GEE) models. In GEE models, measurement data obtained with and without absorptive filters from the two eyes of the same subject were statistically analyzed as repeated measures. Thus, this analysis takes into account the correlated nature of data from the two eyes of the same patient and provides valid P values for mean changes in OCTA parameters from the repeated measurements. In all analyses, a P value < 0.05 was considered to be statistically significant. The Bonferroni correction was used to adjust confidence intervals for multiple comparisons.

Results

Values of SQ without placing the absorptive filter ranged from 5 to 9, the overall mean SQ was 8.25 ± 0.95. The loss of image quality because of the attenuation of light showed a remarkable effect on macular and peripapillary VD measurements, as it is demonstrated in Figure 1 and Figure 2.

Placing a 2.0-mm thick glass plate in between the OCT device and the eye did not result in a significant change of SQ values that supports the conjecture that increased optical path does not have an effect on image quality (Table 1). However, comparing SQ values from the reference measurement without attenuated image quality, the presence of absorptive filters with decreasing light transmittance had a significant negative effect on the corresponding SQ values (Table 1). Next, we calculated a regression line between the light transmittance of the different filters and the corresponding SQ values of the acquired scans. There was a strong correlation between light transmittance and corresponding SQ values for OCTA scans (r = 0.53; $P < 0.001$; Fig. 3).

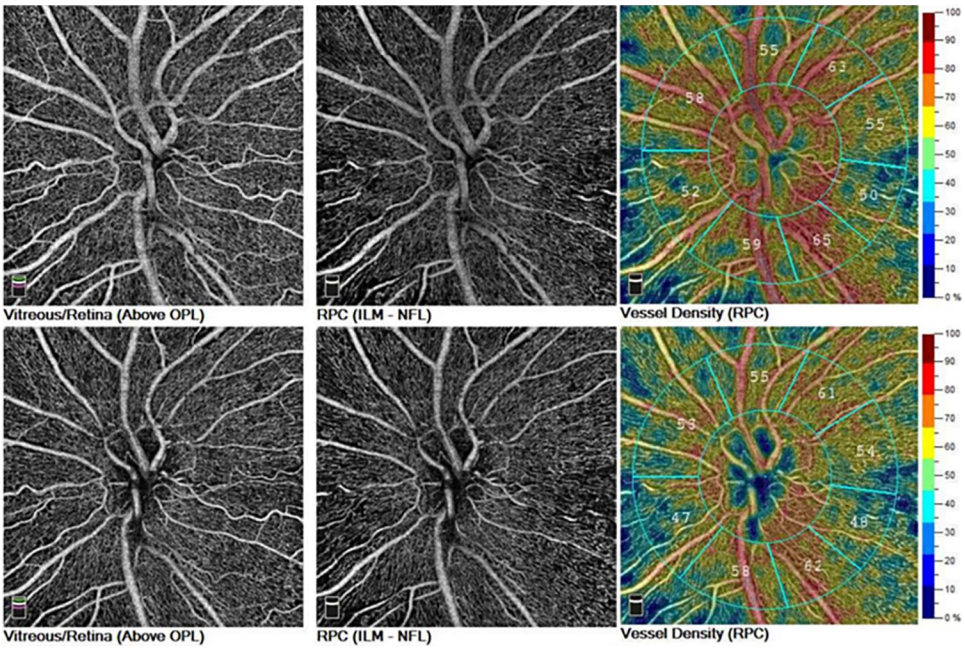

Figure 2. En face OCTA imaging of the optic nerve head in the vitreous/retina and in the radial peripapillary capillaries (RPC) layer, as well as RPC VD (SQ = 8, top row) and by decreasing light transmittance by using an absorptive optical filter OD 0.13 (SQ = 7, bottom row) in the same healthy subject. In addition to the general reduction in the visibility of the disc and peripapillary microvasculature in scans with lower image quality, significant reduction in RPC VD is visible.

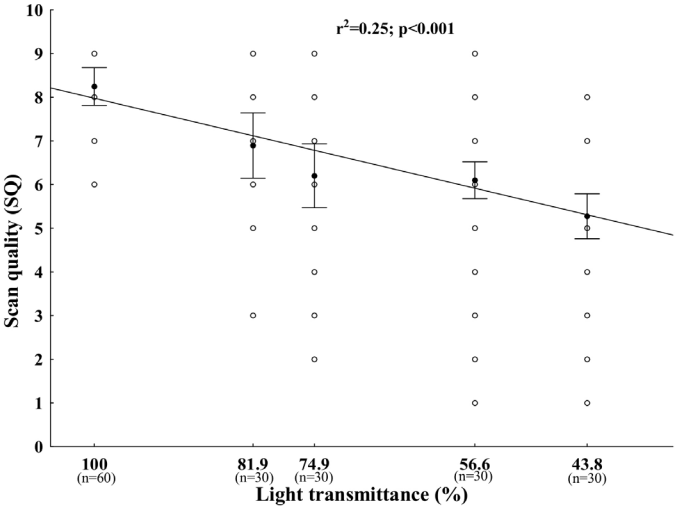

Figure 3. The effect of decreasing light trasmittance on corresponding scan quality (SQ). Note: Bars denote mean ± 95% confidence interval of mean.

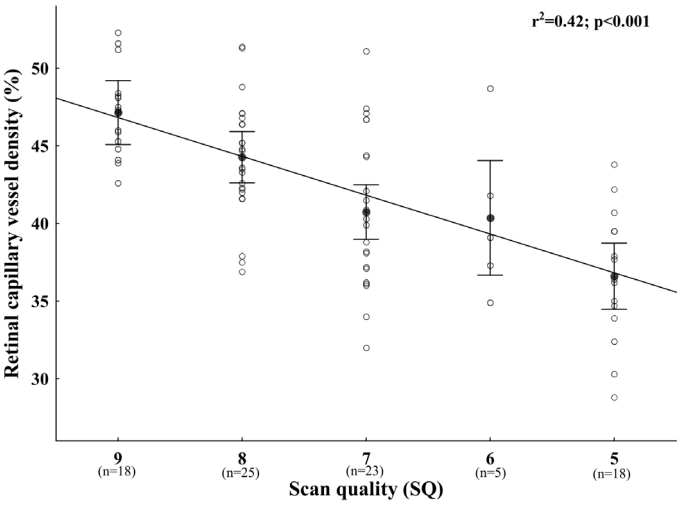

Figure 4. The influence of OCTA scan quality on superficial retinal capillary VD measurements. Note: Bars denote mean ± 95% confidence interval of mean.

OCTA images with lower scan quality were associated with lower retinal VD (Fig. 4).

Finally, we calculated the average changes of OCTA parameters when SQ values of the consecutive scans differed by one unit for the purpose of facilitating comparisons of scans acquired with different image quality. Table 2 shows these uniform correction factors for the different OCTA parameteres adjusted for scan quality between 5 and 10. These correction factors were significant for macular and peripapillary VD measurements except for the peripapillary small VD (Table 2). On the contrary, a one-unit change in image quality did not show any effect neither on NF and FAZ area nor on thickness data (Table 2).

Table 2. The Effect of A One-Unit Change in Scan Quality on OCTA Parameters in The Recommended Range of Image Quality (SQ: 5–10)

Scan Type		Mean	SE	95% CI	*P* Value
OCTA macula	VD superficial layer, %	3.64	0.99	1.69–5.61	<0.001
	VD density deep layer, %	3.05	1.47	0.15–5.94	0.03
	Non-flow area, mm^2	0.03	0.04	−0.06 to 0.13	0.51
	FAZ area, mm^2	0.03	0.04	−0.06 to 0.11	0.53
OCTA optic nerve head	VDAV whole image, %	3.02	1.19	0.69–5.35	0.01
	VDSV whole image, %	2.27	1.17	0.03–4.56	0.04
	VDAV peripapillary, %	3.92	1.67	0.64–7.19	0.01
	VDSV peripapillary, %	2.40	1.51	−0.57 to 5.36	0.11
OCT	Average macular thickness, µm	0.68	2.23	−3.69 to 5.06	0.76
	Foveal thickness, µm	3.98	4.38	−4.59 to 12.56	0.36
	RNFL thickness, µm	9.03	10.44	−11.43 to 29.50	0.39

VDAV, vessel density all vessels; VDSV: vessel density small vessels.
Mean: adjusted for scan quality as a covariate.

Discussion

Our findings demonstrate that OCTA parameters are significantly different in scans with lower image quality compared to those with better quality, despite the fact that all acquired images had acceptable scan quality. The clinical significance of this finding is that in longitudinal patient follow-ups the intra-individual fluctuation is frequent and non-negligible, and, thus, has to be taken into account when interpreting OCTA data.

In general, there are several possible reasons for attenuated image quality, such as media opacities, floaters, blink artifacts, eye saccades, or operator error during image acquisition and these can lead to increased measurement variability. In the elderly population, a cataract is the most common cause of media opacity known to influence the OCT image quality and measurements.[22,27] Because cataract and retinal vascular diseases often coexist in the same eye, progredient clouding of the lens can be a confounding factor in the follow-up of patients using OCTA similar to retinal thickness measurements.[29–37] In this study, we analyzed the correlation among SQ and CRT, RNFL thickness, as well as superficial and deep macular VD, peripapillary VD, NF area and FAZ area, in order to evaluate whether SQ affects OCTA measurements above the recommended threshold. Our findings corroborate those of *Yu* et al. who found that superficial VD measurements are significantly affected by OCT signal strength.[15] In contrast to previous results that reported a positive correlation between image quality and peripapillary RNFL thickness measurements,[38] no correlation between SQ and peripapillary RNFL thickness was found in the present study. One possible explanation for the differing results may have to do with the fact that previous reports included images even with poor scan quality below the advised threshold.[22,39] Another probable reason might be that previous studies applied the signal-to-noise ratio to describe image quality, whereas we used the SQ index that also takes into consideration artifacts from eye motion and defocus.

In our study, the change in image quality could be immediately achieved through placing density filters in front of the eye, eliminating the possible alteration in retinal blood flow—in comparison with other studies where the effect of cataract extraction on OCTA measurements was evaluated. For the purpose of support, the belief that a change in optical path does not have an influence of image quality, OCTA measurements were also performed by placing a glass plate in front of the eye—which was of similar thickness as that of the absorptive filters. This assumption was confirmed by our results, as image acquisition using a clear piece of glass did not produce a significant change in image quality. As the true values of OCTA parameters should be constant during consecutive imaging of the same eye over such a short time, our findings represent only the effect of SQ on OCTA metrics. In other words, by taking OCTA images with and without an absorptive filter shortly one after the other, it is exclusively the difference in light attenuation that can affect the scan quality.[38] Therefore, the association between SQ and superficial macular and peripapillary VD is supposed to be due to the artifactual bias of the SSADA algorithm of the

AngioAnalytics software. Consequently, the present study extends previous results that emphasize: OCTA parameters calculated with different algorithms are not interchangeable,[40–44] thus, longitudinal monitoring of these measurements should be performed with the same instrument,[45] and—as outlined in the results of this study—after compensating for the effect of fluctuations in image quality.

The findings of this study might have several clinical implications because OCTA technology enables us to investigate the retinal microcirculation even before clinical vascular alterations can be observed on fundus examination. As a result, OCTA may prove to be a useful biomarker to aid the early diagnosis and it promises to be useful in monitoring the function and progression of multiple pathologies, such as retinal vascular diseases, glaucoma,[46,47] and preclinical Alzheimer's disease.[48]

Obviously, there are limitations to this study: the acquired data was obtained from healthy subjects using a specific type of device encumbering the generalizability of our results. However, the conclusions derived from our investigations clearly show that a systematic connection does exist between OCT image quality and the measurement results. Further studies with larger cohorts of patients are recommended to validate the correction factors and the associated *P* values. Finally, whereas SQ-adjusted OCTA values are associated with improved comparability of scans, it remains to be examined whether an SQ correction model would ameliorate our ability to follow the progression of diseases affecting retinal microcirculation. Nevertheless, any advancement that improves the ability to detect true changes in retinal microvasculature over time is valuable, and future studies are required to assess the role of compensation for SQ on OCTA metrics in the clinical setting.

In summary, the influence of image quality on OCTA parameters should be considered during patient follow-up using OCTA. We evaluated the effect of image quality on the OCTA parameters in order to make an evaluation of progression more precise because the OCT operator must frequently accept less than ideal scans in real-world practice. For the RTVue OCTA instrument, we suggest the use of a correction factor for each unit change in SQ for VD—even for scans above the recommended SQ cutoff for image comparisons during follow-up. This correction factor would be appropriate for all cases of image degradation—primarily in follow-up studies where the scan does not contain any image artifact, despite the SQ index of the scans differing from the initial ones. In our opinion, the implementation of such a correction factor in the OCTA imaging software might result in an increased accuracy of the assessment of progression and treatment.

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