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ORIGINAL PAPER

Evaluation of the effect of fluorescein angiography on retinal vessel diameter: an optical coherence tomography study

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Abstract
Purpose To evaluate the effect of fluorescein angiography on retinal vessel diameter with Optical Coherence Tomography (OCT).
Methods In this cross-sectional study, a total of 81 eyes of 81 patients who were performed fluorescein angiography (FA) procedure were included. Retinal vessels were examined with the Spectral-domain OCT at baseline and immediately after FA procedure. A cube scan consisting of seven horizontal scans were placed at the inferior border of the disk to include the inferior temporal retinal vessels. Vessels diameters were measured at five measurement points (480–1440 μm inferiorly from the optic disk border).
Results The mean age of the study subjects was 58.02 ± 14.1 years. At baseline, the mean diameter of the retinal artery was 120.16 ± 24.56 μm and of the vein 157.94 ± 32.34 μm at the measurement point of 480 μm, with a gradual decrease to 114.91 ± 25.59 and 152.17 ± 28.17 μm, respectively, at 1440 μm. After FA procedure, the mean diameter of the retinal artery was 122.85 ± 26.35 and of the vein 158.30 ± 32.21 μm at the measurement point of 480 μm, with a gradual decrease to 115.22 ± 22.91 and 151.94 ± 28.93 μm, respectively, at 1440 μm. There were no statistical differences for either of these comparisons at any of the points of both artery and vein measurements.
Conclusion There was not any clinically significant change in retinal artery diameter such as a dilatatory response after FA procedure in patients with hypertension, diabetes, and age-related macular degeneration (AMD).

Keywords Fluorescein angiography · Optical coherence tomography · Retinal vessel diameter

Introduction

The retinal blood vessels are the only part of the central circulation system that can be directly and noninvasively visualized. The diameters of retinal blood vessels are considered as an important indicator of both cardiovascular and cerebrovascular diseases and the diameter measurement has become a subject of extensive research [1–4].

With the development of fundus imaging techniques, several methods have been described for the measurement of retinal vessel diameters, most of them using retinal photography and computer-assisted image analysis [5, 6]. In addition, fluorescein angiography (FA) [7], dynamic vessel analyzers [8], and scanning laser ophthalmoscopes [9] have all been used to evaluate the diameters of retinal vessels.

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Spectral-domain optical coherence tomography (SD-OCT) has become a widespread imaging modality in various retinal diseases. This cross-sectional imaging technology provides high-resolution scans that resemble in vivo histology and allows investigators to image the retina and vasculature in perpendicular sections. On OCT, retinal vessels appear as hyperreflective features in the inner retina [10]. The characteristics of retinal vessels have already been studied on OCT [11, 12].

Fluorescein angiography has contributed greatly to the diagnosis and treatment of many common chorioretinal diseases. Technological advances in digital imaging and computer analysis have further expanded the clinical and research applications of FA [13]. To the best of our knowledge, no study has attempted to assess the direct effects of FA on retinal vessel diameters.

The purpose of the current study was to evaluate the effect of FA on retinal vessel diameter in patients with hypertension, diabetes, and age-related macular degeneration (AMD), and therefore help to better understand these disease's effects on the retinal vessel diameters independently of the effects of fluorescein, if there exists any.

Methods

The ethics committee at Erciyes University School of Medicine approved this cross-sectional study, which was conducted in accordance with the tenets of the declaration of Helsinki. Written informed consent was obtained from each subject before any study procedures or examinations were performed. All of the subjects were recruited between June and November 2015.

Patients

This cross-sectional study included 81 eyes from 81 subjects at the Erciyes University Department of Ophthalmology, Division of Retina who were performed FA procedure for various retinal pathologies (diabetic retinopathy, hypertensive retinopathy, age-related macular degeneration). Retinal vessels were examined with the Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). A single eye was chosen randomly for inclusion in the study. Where the image quality was not of sufficient quality for measurement, the other eye was included.

Eyes that had any of the followings were excluded from the study: keratoconus, high myopia (more severe than -6 diopters), high astigmatism (more severe than ± 3 diopters), prior intraocular surgery, or coexisting ocular disease (i.e., glaucoma, senile cataract resulting in poor-quality OCT images). Subjects with systemic disease (i.e., stroke, ischemic heart disease, collagen disease, renal disease/failure, migraine), except for diabetes or hypertension, were also excluded. Diabetic retinopathy severity was graded on the basis of clinical examination and categorized into mild nonproliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, and proliferative diabetic retinopathy (PDR) on the basis of the modified Airlie House/Early Treatment Diabetic Retinopathy Study (ETDRS) criteria [14]. Diabetic participants were chosen from the patients with mild NPDR; patients with severe NPDR and PDR and glycosylated hemoglobin A1c (HbA1c) $>7\%$ were excluded. The patients who had hypertension history over 10 years and systolic blood pressure (BP) ≤ 140 mm Hg or a diastolic BP ≤ 90 mm Hg with anti-hypertensive therapy were included in this study. Also for the hypertensive participants, patients with uncontrolled arterial hypertension were excluded. All AMD patients had dry AMD. All diabetic, hypertensive, and AMD patients were treatment naive for intravitreal injection. Blood pressure measurement was taken at the same time as FA imaging.

All participants were examined through dilated pupils. Fluorescein angiography was performed by means of a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph; Heidelberg Engineering, Heidelberg, Germany) after injection of an intravenous dose of 5 ml of 10% sodium fluorescein (Fluorescein 10%; Novartis Pharma, Bern, Switzerland). Retinal vessel measurement was performed using the SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) with a ~ 840 nm wavelength. Three consecutive measurements were performed at baseline and five minutes after fluorescein angiography procedure. The averaged value from three consecutive measurements was used for statistical analysis.

Measurement of blood vessels

A cube scan consisting of seven horizontal scans were placed at the inferior border of the disk to include the large retinal vessels originating from the disk (inferior temporal retinal arcades) (Fig. 1). The scans were 20° or 30° in size and of high resolution, 100 Automatic Real Time (ART) for maximal quality and resolution, and had a 240 µm interscan interval. Because the cube was placed at the optic disk border, each raster (from 1 to 7) was placed at a known constant distance from the optic disk border (Rasters 1–7 were at distances of 0, 240, 480, 720, 960, 1200, and 1440 µm, respectively). The eye-tracking system and the averaging technique (both unique features of the Spectralis) were used to ensure high quality and reduction of noise speckles. Each measurement was carried out on each of the OCT raster images from the hyperreflective signal inferiorly to the hyperreflective signal superiorly (i.e., lumen plus vessel walls) as described previously [15–17] (Fig. 1). Difficulties in identifying the border of the retinal vessels at the first and second raster line (i.e., at the optic disk border and at 240 µm) led to the exclusion of those two rasters. Therefore, the statistical analysis was conducted only on the measurements of Lines 3 to 7 inferiorly (480–1440 µm from the optic disk border). Vessels in which these landmarks were not distinguishable were excluded from analysis. The mean diameter of the arteries and veins was then calculated separately for each of the rasters and each of the measurements (Fig. 2).

Masked retinal specialists independently (DGS, MU) measured vessel diameters on each OCT scan.

Statistical analysis

SPSS version 16 for Windows (Chicago, IL, USA) was used for statistical analysis. Descriptive data were presented as mean and standard deviation and percentages. The data were tested for normal distribution using the Kolmogorov–Smirnov test. To compare retinal vessel diameter measurements at baseline and 5 min after FA procedure, the nonparametric test of Wilcoxon was considered. The Kruskal–Wallis test was used to compare subgroup analyses of retinal diseases. Finally, a Pearson correlation coefficient test was performed to compare the mean retinal artery and vein diameters for all the measurement points. P values of <0.05 were considered significant for statistical test.

Results

Patients

Eighty-one eyes of 81 patients were included in this study. The mean age was 58.02 ± 14.1 years. Table 1 presents the systemic and ocular characteristics for the subjects included in the study. The best-corrected visual acuity of all eyes ranged between 20/20 and 20/30. The biomicroscopic examination of the anterior segments and the macular OCT scan were within normal limits for all participants.

Diameters of the arteries

At baseline, the mean diameters of the arteries of the 81 participants at 480 µm from the optic disk (Raster

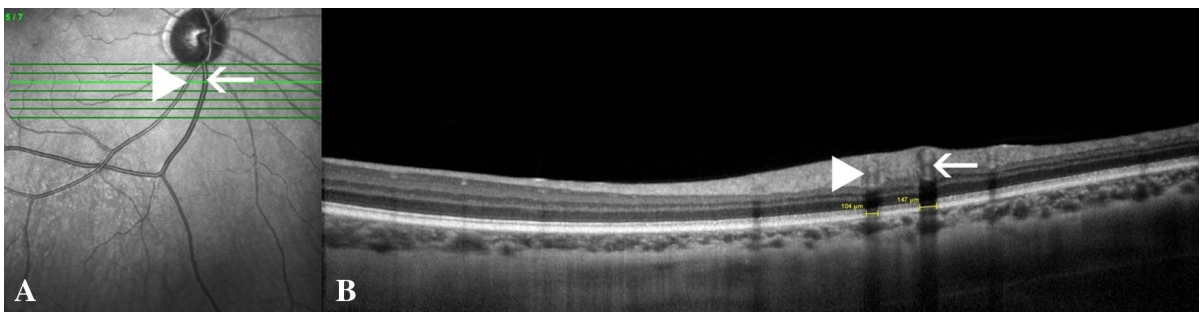

Fig. 1 Image of the retinal vessels before FA. **a** A cube scan composed of seven horizontal rasters with a 240 µm interscan interval including the inferior temporal retinal vessels. The first raster is located at the inferior edge of the optic disk. **b** Image corresponding to the raster scan visible in the infrared image. The *arrow* and *arrow head* indicate the retinal veins and retinal arteries, respectively

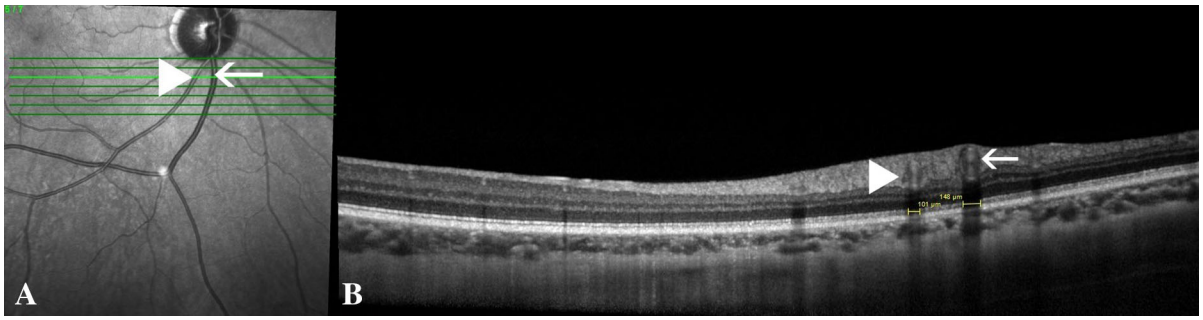

Fig. 2 Image of the retinal vessels after FA. **a** Horizontal rasters including the inferior temporal retinal vessels. **b** Image corresponding to the raster scan visible in the infrared image. The *arrow* and *arrow head* indicate the retinal veins and retinal arteries, respectively

Table 1 Systemic and ocular characteristics of optical coherence tomography study subjects

	Hypertension group (*n*: 25 eyes)	Diabetes group (*n*: 25 eyes)	AMD group (*n*: 31 eyes)
Age (year, mean ± SD, range	56.8 ± 13.3	58.8 ± 13.07	58.4 ± 13.5
Sex (male/female)	11/14	12/13	15/16
Hypertension (±)	25/0	0/25	0/31
Diabetes (±)	0/25	25/0	0/31
Dyslipidemia (±)	15/10	16/9	20/11
Systolic blood pressure (mm Hg)	132.7 ± 12.2	127.4 ± 13.1	128.7 ± 14.2
Intraocular pressure (mm Hg)	12.8 ± 3.4	13.4 ± 2.1	13.1 ± 2.3
Refractive error (diopters, mean ± SD)	0.0 ± 1.8	0.0 ± 2.1	0.0 ± 1.9

3) were 120.16 ± 24.56 μm, with a steady decline to 114.91 ± 25.59 at 1440 μm (Raster 7), the last measurement point. After FA procedure, the mean diameters of the arteries was 122.85 ± 26.35 μm at 480 μm and 115.22 ± 22.91 μm at 1440 μm (Table 2). There were no statistical differences for either of these comparisons at any of the points of measurement ($P > 0.05$).

The mean results of patients with hypertension, diabetes, and AMD are presented in Table 3. There were no statistical differences for either of these comparisons at any of the points of measurement in diabetes, hypertension, and AMD groups ($P > 0.05$).

Hypertensive patients had narrower mean artery diameter measurements at all measurement points than diabetic and AMD patients before and after FA

Table 2 Retinal artery and vein diameter measurements (mean ± SD in μm) at baseline and after FA

	Mean artery diameter (*n*: 81 eyes)			Mean vein diameter (*n*: 81 eyes)		
	Baseline	After FA	*P* value	Baseline	After FA	*P* value
Raster 3	120.16 ± 24.56	122.85 ± 26.35	0.32	157.94 ± 32.34	158.30 ± 32.21	0.88
Raster 4	119.37 ± 22.96	119.45 ± 26.16	0.87	156.01 ± 29.80	156.25 ± 31.20	0.85
Raster 5	116.30 ± 22.76	117.36 ± 26.63	0.66	155.50 ± 26.06	155.41 ± 27.75	0.74
Raster 6	115.33 ± 28.76	116.63 ± 30.12	0.63	152.76 ± 28.70	154.92 ± 32.87	0.29
Raster 7	114.91 ± 25.59	115.22 ± 22.91	0.73	152.17 ± 28.17	151.94 ± 28.93	0.95

Wilcoxon test, *P* value <0.05 was considered statistically significant

Table 3 Retinal artery diameter measurements (mean ± SD in μm) at baseline and after FA in various retinal diseases

	Hypertension group (*n*: 25 eyes)			Diabetes group (*n*: 25 eyes)			AMD group (*n*: 31 eyes)		
	Baseline	After FA	*P* value	Baseline	After FA	*P* value	Baseline	After FA	*P* value
Raster 3	116.05 ± 23.11	114.13 ± 33.95	0.42	123.88 ± 27.60	122.66 ± 24.77	0.88	125.32 ± 21.15	125.18 ± 20.66	0.94
Raster 4	115.60 ± 18.50	115.67 ± 18.57	0.97	120.09 ± 28.04	118.89 ± 28.74	0.77	120.23 ± 22.34	121.33 ± 29.69	0.29
Raster 5	113.62 ± 22.16	114.39 ± 22.30	0.38	118.40 ± 23.53	117.62 ± 27.22	0.85	118.20 ± 23.06	120.98 ± 29.42	0.63
Raster 6	112.17 ± 29.87	113.28 ± 33.46	0.30	117.21 ± 31.98	118.93 ± 33.98	0.52	117.33 ± 25.14	118.07 ± 24.38	0.60
Raster 7	111.25 ± 31.26	112.21 ± 30.53	0.49	116.04 ± 24.68	117.55 ± 30.26	0.42	116.96 ± 21.62	118.29 ± 28.92	0.54

Wilcoxon test, *P* value <0.05 was considered statistically significant

procedure ($P = 0.01$, $P = 0.01$; respectively) (Table 3).

Diameters of the veins

At baseline, the mean diameters of the veins of the 81 participants at 480 μm from the optic disk (Raster 3) were 157.94 ± 32.34 μm, and 152.17 ± 28.17 μm at 1440 μm (Raster 7), the last measurement point. After FA procedure, the mean diameters of the veins was 158.30 ± 32.21 μm at 480 μm and 151.94 ± 28.93 μm at 1440 μm (Table 2). There were no statistical differences for either of these comparisons at any of the points of measurement ($P > 0.05$).

Table 4 displays the results of comparisons between the mean diameters of the veins between baseline and after FA procedure. There were no statistical differences for either of these comparisons at any of the points of measurement in hypertension, diabetes, and AMD groups ($P > 0.05$).

Diabetic patients had wider mean vein diameter measurements at all measurement points than hypertensive and AMD patients before and after FA procedure ($P = 0.001$, $P = 0.001$; respectively) (Table 4).

None of the patients had severe adverse reaction (laryngeal edema, bronchospasm, cardiac arrest, or seizures) to FA. Eight of 81 patients (9.8%) had transient nausea during FA.

Discussion

This is the first study that clarified the effect of fluorescein angiography on retinal vessel diameter with commercially available SD-OCT. We found that there was not any change in retinal vessel diameter or a dilatatory response, either for arterioles or venules after FA procedure at several retinal diseases including AMD, diabetes, and hypertension. Using SD-OCT, the diameters of the retinal vessels could be determined accurately.

Fluorescein sodium is a water-soluble ophthalmologic diagnostic substance with a negligible binding affinity to any vital tissue, which accounts for its low toxicity. It is freely and widely distributed into ocular structures by diffusion; however, active transport is needed to reach the retina [18]. Adverse reactions to

Table 4 Retinal vein diameter measurements (mean ± SD in μm) at baseline and after FA in various retinal diseases

	Hypertension group (*n*: 25 eyes)			Diabetes group (*n*: 25 eyes)			AMD group (*n*:31 eyes)		
	Baseline	After FA	*P* value	Baseline	After FA	*P* value	Baseline	After FA	*P* value
Raster 3	147.06 ± 30.21	150.96 ± 33.94	0.16	161.25 ± 38.57	162.39 ± 38.59	0.24	145.64 ± 27.0	150.92 ± 24.23	0.16
Raster 4	146.52 ± 27.35	149.34 ± 25.57	0.23	159.65 ± 33.05	157.75 ± 33.70	0.81	145.35 ± 27.88	143.85 ± 32.21	0.76
Raster 5	144.00 ± 25.18	148.08 ± 26.30	0.64	158.92 ± 27.20	156.52 ± 27.11	0.27	143.01 ± 24.31	142.04 ± 28.65	0.58
Raster 6	143.28 ± 28.32	147.60 ± 28.36	0.11	153.63 ± 22.42	158.99 ± 33.36	0.70	142.70 ± 32.06	141.77 ± 35.41	0.29
Raster 7	143.81 ± 26.72	147.67 ± 29.84	0.54	154.60 ± 29.85	157.56 ± 31.99	0.96	141.32 ± 27.81	140.86 ± 25.66	0.59

Wilcoxon test, *P* value <0.05 was considered statistically significant

FA range from mild to severe and include nausea, sneezing, pruritus, urticaria, syncope, pyrexia, nerve palsy, local tissue necroses, laryngeal edema, bronchospasm, cardiac arrest and seizures. Some of these reactions may well involve mast cell activation. Others may involve a vasovagal response, anxiety-related sympathetic discharge, toxic effect, vasospasm, complement activation and idiosyncratic reactions [13, 19]. Because of these previously known effects of fluorescein, we hypothesized that fluorescein might also have a vasodilatory or vasoconstrictive effect on retinal vessels.

The fluorescein permeability index obtained from the vitreous was shown to increase with the increasing degree of retinopathy [20]. A significant elevation was observed in diabetics with background and proliferative retinopathy. The breakdown of the blood retinal barrier might be a primary alteration of the blood retinal barrier itself or initially an altered ocular blood flow followed by an affection of the barrier. Fluorescein kinetics in diabetic subjects is altered in the anterior segment as well as the posterior part of the eye. These alterations seem to be a manifestation of a generalized disease process in the entire diabetic individual. In any part of the diabetic organism, basement membrane alterations including thickening might be of primary importance in understanding generalized diabetic tissue affection [20]. Recently, Shao et al. evaluated retinal vessel diameter changes in different severities of diabetic retinopathy by SD-OCT. They reported that wider retinal venule diameter was significantly associated with the severity of NPDR [21]. Similarly, in this study diabetic patients had wider mean vein diameter measurements at all measurement points than hypertensive and AMD patients before and after FA procedure ($P = 0.001$, $P = 0.001$; respectively).

In our group of diabetes, there were no statistical differences neither for arterioles nor venules after FA procedure at any of the points of measurement. However, this is expected because most of the patients in the diabetes group were in the early stages of diabetes without retinopathy. This group of diabetic patients was specifically chosen, because we aimed to show the nude effect fluorescein in these patients independently of the fluorescein leakage cause by diabetic vasculopathy.

Mendrinos et al. reported the effect of intravitreal ranibizumab on the retinal arteriolar diameter in patients with neovascular AMD [22]. They suggested

that intravitreal ranibizumab induces sustained retinal arteriolar vasoconstriction in eyes with neovascular AMD [22]. In our study, there were no statistical differences either for arterioles or venules after FA procedure at any of the points of measurement in AMD group.

Schuster et al. investigated OCT-based retinal vessel analysis for the evaluation of hypertensive vasculopathy, and found a relation between mean arterial blood pressure and OCT-based A/V ratio was established [23]. A recent OCT study examined the cross-sections of retinal vessels on peripapillary OCT scan and showed that the wall thickness of retinal vessels correlates with age and is different in hypertensive and normotensive patients [24]. In our study, especially the deep boarder of the vessel was often not sufficiently identifiable due to OCT signal attenuation and we therefore did not perform wall thickness measurements. Hypertensive patients had narrower mean artery diameter measurements at all measurement points than diabetic and AMD patients before and after FA procedure ($P = 0.01$, $P = 0.01$; respectively). There were no statistical differences either for arterioles or venules after FA procedure at any of the points of measurement in hypertensive patients.

Exact measurement of retinal vessel diameter with SD-OCT is a new diagnostical option, meaningful especially in patients with vascular diseases. Fluorescein Angiography (FA) theoretically might have an impact on the vessel diameter within the course. Even there is an effect on the vessels during FA, it is only a short-time effect. For the effect, severity of the diseases is more important. The usefulness of this study is to show that the diameter of retinal vessels parapapillar can be measured exactly and repeatedly, and FA does not change the vessel diameter.

To our knowledge, this is the first study in the literature on the direct effects of fluorescein on the retinal vascular diameters in different retinal disease groups. Our study had limitations in terms of a small sample size and the lack of a healthy control group. However, as this is a clinical study rather than experimental, it is not possible to perform angiography procedure to the healthy patients. Additionally, prospective research into the different stages of diabetic and hypertensive retinopathy is recommended.

In conclusion, there was not any clinically significant change in retinal artery diameter such as a dilatatory response after FA procedure in patients with hypertension, diabetes, and AMD.

Compliance with ethical standards

Conflict of interest None of the authors has conflict of interest with this submission.

Financial disclosure None of the authors has financial interest in any material or method mentioned.

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