# Optical Coherence Tomography Angiography Quantitative Assessment of Exercise-Induced Variations in Retinal Vascular Plexa of Healthy Subjects

Sétha Vo Kim,[1] Oudy Semoun,[1] Alexandre Pedinielli,[1] Camille Jung,[2] Alexandra Miere,[1] and Eric H. Souied[1,2]

[1]Department of Ophthalmology, Centre Hospitalier Intercommunal de Créteil, University Paris Est Créteil, Créteil, France
[2]Clinical Research Center, GRC Macula, and Biological Resources Center, Centre Hospitalier Intercommunal de Créteil, Créteil, France

Correspondence: Eric H. Souied, Department of Ophthalmology, Centre Hospitalier Intercommunal de Créteil, Université de Paris Est Créteil, 40 Avenue de Verdun, 94000 Créteil, France; eric.souied@chicreteil.fr.

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**Purpose.** To assess the variations induced by exercise in retinal vascular density (VD), foveal avascular zone (FAZ) area, and fractal dimension (FD) at the superficial (SCP) and deep (DCP) capillary plexa in healthy subjects by means of optical coherence tomography angiography (OCT-A).

**Methods.** Consecutive healthy subjects were prospectively included into two groups, ranging in age from 18 to 29 years for group 1 and from 30 to 40 years for group 2. Data from 3 × 3-mm OCT-A acquisition centered on the macula at SCP and DCP (VD, FAZ area, and FD), heart rate, and systolic-diastolic blood pressure were collected before and after a 20-minute standardized physical exercise on a stationary bicycle.

**Results.** Both eyes of 32 healthy volunteers were prospectively included (15 in group 1 and 17 in group 2). Mean age was 27 ± 7 years. In the overall analysis and for each group, a decrease of VD at the level of SCP and an increase of FD at the level of DCP were significant after exercise. A significant correlation was found between these modifications of retinal vascularization and the increase of systolic blood pressure induced by exercise. All cardiovascular parameters increased significantly with exercise. No significant difference was found between the two groups, and no incident was reported.

**Conclusions.** A significant correlation was established between systemic cardiovascular modifications (reflected by systolic blood pressure) and local retinal vascularization changes at SCP during exercise. A rest period might be recommended before OCT-A data acquisition, as modifications of cardiovascular parameters could distort retinal vascular data.

Keywords: optical coherence tomography angiography, exercise, macular vascular density, foveal avascular zone, fractal dimension

Intense exercise involves anaerobic metabolism and increased oxygen consumption, and induces systemic vascular changes.[1] It is associated with an increase of heart rate and cardiac blood flow, with a strategic redistribution, such as vasodilatation of vessels intended for heart and skeletal muscles, whereas vasoconstriction is observed for skin and splanchnic tissues. This regulation is under the control of neurologic factors (activation of sympathetic nerve system, at the expense of the parasympathetic nervous system) and metabolic factors released by active cells.[2–7]

Optical coherence tomography angiography (OCT-A) is a dyeless noninvasive method of imaging the retinal microvasculature in the posterior pole. With the advent of normative databases on OCT-A for vascular density (VD) and foveal avascular zone (FAZ) area of healthy adult,[8,9] OCT-A appears to be a useful tool for change analysis in both healthy eyes and eyes with macular diseases, with an excellent reproducibility and repeatability of measurements.

Consequently, this imaging technique has been widely used in the last years to assess microvascular damages in diabetic retinopathy and maculopathy,[10–12] retinal vein occlusion,[13,14] as well as for choroidal neovascularization detection and follow-up and/or outer retinal and choriocapillaris perfusion.[15–18]

Unlike conventional fluorescein angiography (FA), OCT-A is depth resolved and thus allows the noninvasive separate assessment of the three plexa previously described in histologic studies, namely, superficial, intermediate, and deep capillary plexa.[19]

With high oxygen demand due to intense cellular activity, the retina is densely vascularized, with a complex vessel distribution. The three plexa of retinal microvasculature provide the metabolic needs (nutrients and oxygen) for the inner retinal layers, whereas the choriocapillaris ensures vascularization of the external retinal layers. While choroidal vascularization is controlled by sympathetic innervation, retinal vascularization is self-regulated, and is under the influence of local factors released by endothelial cells.[20,21] Variations in retinal microvasculature after exercise might therefore be expected and could have an impact on the results of the examination. These variations may be assessed in terms of VD, but also by using more complex mathematical concepts, such as fractal dimension (FD).

The complex geometric patterns found in the retinal vessels can be described by the FD, which provides a quantitative and accurate description of self-similarity and scaling.[22] Fractal analysis has already been used to explore the retinal vasculature in several studies, using fundus photography,[23–26] FA,[27,28] or OCT-A.[29,30]

To the best of our knowledge, there is no anatomic data available, analyzing the effects of physical exercise in healthy subjects, on the retinal VDs, FAZ area, and retinal vascular FD in vivo using OCT-A at the same time. Variations in microretinal vasculature, which might be expected, could have an impact on the results of the examination.

The aim of this study was to assess the variations of OCT-A measurements on the macular area, after physical exercise, in order to identify a potential impact on their reliability in everyday medical practice and in medical research.

## Methods

Healthy volunteers aged 18 to 40 years, with no past medical history, were included in this prospective study at the Créteil University Hospital between June 2016 and September 2016. Exclusion criteria were asthma, respiratory or cardiovascular failure, arthritis, as well as macular diseases on fundus examination. Participants were healthy and had a sedentary lifestyle. To evaluate age-related data, the study population was divided into two age groups: group 1 ranged from 18 to 29 years of age, group 2 ranged from 30 to 40 years. We compared measures of VD (whole, parafoveal, and foveal), FAZ area, and FD parameters before and after physical effort.

The study was conducted in accordance with the tenets of the 1964 Declaration of Helsinki. Informed consent was obtained from all the study subjects, after presentation of the study protocol.

For all patients, slit-lamp biomicroscopy and fundus examination were carried out, to exclude blurred intraocular media and preexisting macular diseases.

### OCT-A Angiography

All patients underwent OCT-A imaging before physical exertion at rest, and immediately after 20 minutes of biking. Central macular 3 × 3-mm scans were performed with the AngioVue Imaging System Optovue RTVue XR 100 Avanti with the software AngioVue OCTA, system version 2015.100.0.35 (Optovue, Inc., Fremont, CA, USA). The scan speed was 70,000 A-scans per second, using a light source centered on 840 nm and a bandwidth of 45 nm. Each 3 × 3-mm OCT-A volume contains 304 × 304 A-scans, completed by two consecutive orthogonal B-scans at each position, to minimize motion artifacts.

The same examiner collected three measurements on the same device before and after exercise, and the average of these measurements was performed. Only high-quality images with a signal strength of at least 60 were retained (according to the manufacturer's image-quality scale). Default automatic segmentation distinguished between the superficial capillary plexus (SCP) from 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer (IPL), while the offset for the deep capillary plexus (DCP) extended from 15 to 70 μm below the IPL. The VD and FAZ area at the level of SCP and DCP have been collected.

### Vascular Density

We used the embedded software AngioAnalytics of the OCT-A device to analyze the VD in the SCP and DCP (%) and the FAZ area. VD is calculated as the percentage area occupied by flowing blood vessels in the selected region. A binary vessel image is extracted from the OCT-A en face image, and VD is then deduced by the percentage of white pixels of vessels in the defined sectors on the binary image.

### Fractal Dimension

The OCT-A SCP and DCP flow images generated by automatic segmentation were extracted in raw format and further processed with ImageJ (http://imagej.nih.gov/ij/; Wayne Rasband, provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). We used the macro design described in a previous study[31] and applied it into all OCT-A images.

The vessel maps (16-bit) were then skeletonized with the ImageJ skeletonizing algorithm ImageJ software and converted to tiff format, as shown in Figure 1. After image processing, FD analysis was performed on the skeletonized images of both the superficial and deep retinal capillary plexa. The quantitative measured parameter of FD was obtained with the fractal analysis toolbox from Fractalyse software (ThéMA, Burgundy, France). The standard box–counting method was used: the skeletonized images were divided into a large number of equally sized square boxes (maximum size of 128 pixels to avoid an edge effect), and the number of boxes containing a section of the skeletonized line is counted; the process is then repeated with a differently sized box.

Fractal analysis was performed on the total parafoveal area with a diameter of 3 mm, as in a previous study.[30] FDs of the SCP and DCP were compared before and after exercise.

Raw and tiff formats were used as these do not incur destructive image compression, unlike jpeg format.

### Stress Protocol

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate levels were monitored at rest after 10 minutes of being seated, and on the bike at 5, 10, 15, and 20 minutes of exercise, by using a standard blood pressure cuff on the left arm at heart level. Oxygen saturation at rest was collected by using a pulse oximetry sensor, placed on the fingertip.

Physical exertion consisted of continuously riding 20 minutes on a training bike (Elite 105; Schmidt Sportsworld, Essen, Germany), with an increase of the resistance level every minute, from level 1 to 8. Our exercise protocol was determined as follows: a warm-up period of 5 minutes at a moderate speed (9 mph, 15 km/h) with the lowest resistance, then the scheduled level of resistance was increased every minute during 15 minutes. At each level, the pedalling speed must be constant. This 1-minute incremental stress protocol has been inspired from cardiologic effort trials (triangular protocol[31–34]). The final pedalling speed must be at least 15 mph (25 km/h).

All patients reached 85% of maximum theoretical heart rate, the latter being defined by the following equation: (220 − Age). In this way, exercise was considered as maximal in cardiologic terms, as specified in most cardiologic stress protocols.[35]

The mean arterial pressure (MAP) was obtained by applying the following equation: MAP + (SBP + 2 × DBP)/3.[36]

Exercise was discontinued in case of intense discomfort or intense dyspnea. There was no recovery period, as we wanted to collect data as close as possible to exercise.

Data were separately analyzed by two independent experts (SVK, AM). In case of a disagreement, a third expert (EHS) settled the situation. A global analysis concerned the entire study population; a subgroup analysis was also performed between group 1 (18–30 years) and group 2 (30–40 years).

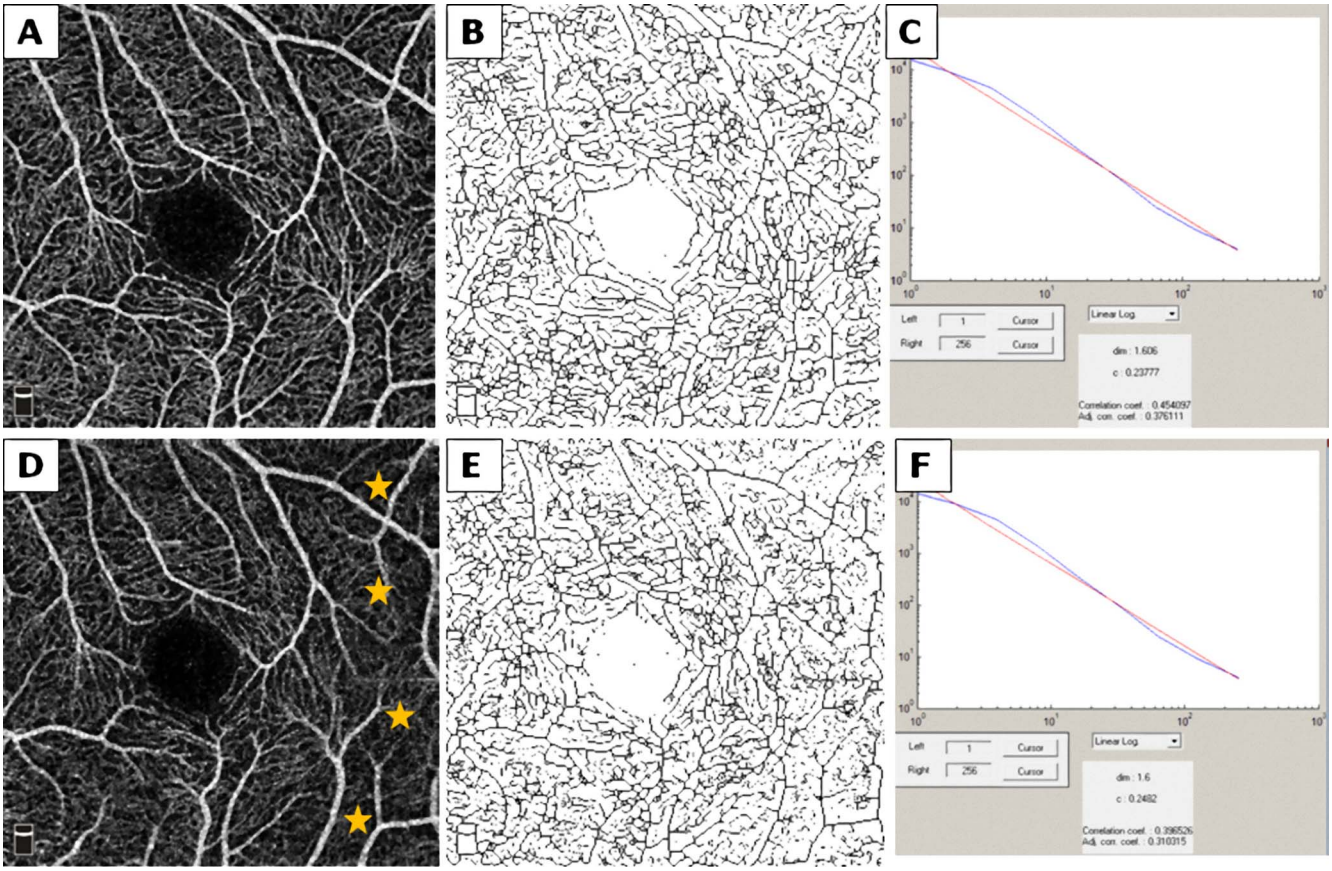


FIGURE 1. Optical coherence tomography angiography of the left eye of a 31-year-old man: comparison before/after exercise at the level of superficial capillary plexus. *Top*: Before exercise. (**A**) Original 3 × 3-mm OCT-A acquisition of the superficial capillary plexus centered on the fovea. (**B**) After binarization and skeletonization with ImageJ. (**C**) Fractal analysis using Fractalyse. *Bottom*: After a 20-minute exercise. (**D**) Original 3 × 3-mm OCT-A acquisition of the superficial capillary plexus centered on the fovea, just after a 20-minute exercise. (**E**) After binarization and skeletonization with ImageJ. (**F**) Fractal analysis using Fractalyse. The *blue line* represents OCT-A data for this image; the *red line* represents the closest fitting fractal log-log line. The *x*-axis corresponds to the log base 10 of the size of the boxes (in pixels); the *y*-axis represents the log base 10 of the number of boxes covering the OCT-A pattern. The fractal dimension is calculated by linear regression: $\log(y) = \log(x) * \dim + c$. The *c* represents coefficient of correlation of fractal measurements, which estimates the accuracy of calculated fractal values. We can observe on the OCT acquisition after exercise (**D**) a mild rarefaction of the vascularization in the temporal parafoveal zone (*yellow stars*), while the foveal zone remains stable. The calculated fractal dimension remains identical.

### Statistical Analysis

Statistical analysis was performed by using STATA software (version 13; STATACORP, College Station, TX, USA) and included descriptive statistics for main clinical features. Wilcoxon test was used to compare quantitative data. For all findings, the chosen level of statistical significance was $P < 0.05$. OCT-A quantitative parameters, such as VD and FD at baseline and follow-up, were compared with functional and anatomic data at baseline and last follow-up visit, in order to establish an association between these OCT-A quantitative criteria and clinical outcomes.

Bland-Altman plot, intraclass correlation (ICC), and coefficient of repeatability (CR) were used to evaluate the agreement between the measurements.

## RESULTS

We prospectively included 64 eyes of 32 healthy volunteers (11 men and 21 women), aged from 18 to 40 years, between June 2016 and October 2016. Thirty eyes were included in group 1 (7 men/8 women between 18–30 years of age, mean age: 20.6 years), and 34 eyes in group 2 (4 men/13 women between 30–40 years old, mean age: 33.5 years).

### Quantitative Analysis

At the level of SCP, there was no significant difference in the foveal VD before and after physical exertion (before: 30.99% ± 6.3%; after: 31.1% ± 6.2%). However, a statistically significant decrease in the whole and parafoveal VD was identified, from 54.9% ± 2.7% to 52.3% ± 2.7% and from 57.5% ± 3.1% to 55.1% ± 3%, respectively ($P < 0.0001$). These findings are presented in Table 1. Our own repeatability (ICC, CR) was excellent at the level of SCP in whole and parafoveal areas (Table 2).

Central avascular area remained stable (Table 3), as well as FD (Table 4). At the level of DCP, there was no significant difference in VD and FAZ area. Conversely, the FD increased significantly from 1.68 to 1.69 ($P < 0.0001$).

The subgroup analysis between groups 1 and 2 did not reveal any significant difference, before and after exercise, in VD, FAZ area, and FD ($P = 0.2$, $P = 0.4$, and $P = 0.2$, respectively).

### Cardiovascular Parameters

After exercise, SBP, DBP, MAP, and heart rate increased significantly, from 118 ± 8.6 to 167.8 ± 13.8 mm Hg, from

**Table 1.** Variation of Vascular Densities After Exercise in the Superficial and Deep Plexa in the Overall Study Population: Estimated Mean Change and Its 95% CI

| Vascular Densities | Before Exercise | After 20 Minutes of Exercise | *P* |
|---|---|---|---|
| Superficial plexus | | | |
| Whole, % | 54.9 | 52.3 | **<0.0001** |
| | 95% CI (54.2–55.6) | 95% CI (51.7–53) | |
| Foveal, % | 31 | 31.1 | 0.81 |
| | 95% CI (29.4–32.6) | 95% CI (29.6–32.7) | |
| Parafoveal, % | 57.5 | 55.1 | **<0.0001** |
| | 95% CI (56.8–58.3) | 95% CI (54.3–55.8) | |
| Deep plexus | | | |
| Whole, % | 59.3 | 58.8 | 0.07 |
| | 95% CI (58.8–59.8) | 95% CI (58.2–59.3) | |
| Foveal, % | 28.2 | 28.2 | 0.08 |
| | 95% CI (26.4–30.1) | 95% CI (26.3–30.1) | |
| Parafoveal, % | 62.5 | 61.9 | 0.09 |
| | 95% CI (62–62.9) | 95% CI (61.3–62.5) | |

Bold values indicate statistical significance $P < 0.05$.

70.4 ± 6 to 82 ± 5.9 mm Hg, from 86.3 ± 5.5 to 110.7 ± 6.9 mm Hg, and from 76.9 ± 8.7 to 182.8 ± 5.7 bpm, respectively ($P < 0.0001$; Fig. 2).

There was no significant difference concerning the cardiovascular parameters at baseline and after physical exertion between groups 1 and 2.

None of the included patients disrupted exercise because of an intense discomfort. No incident was reported during the exercise. All patients had an oxygen saturation that exceeded 98% before exercise, but unfortunately it was not possible to obtain a reliable measure during exercise.

VD at the level of SCP (whole and parafoveal) was significantly correlated to the SBP (Pearson correlation coefficient –0.74 and –0.66, respectively; $P < 0.0001$) (Figs. 3, 4; Table 5).

## Discussion

In our study, variations of retinal microvascularization in OCT-A were assessed in healthy subjects, before and after physical exertion.

On the one hand, we highlighted significant decrease of VD at the level of SCP. This variation observed at the level of SCP was more important than the described intrinsic fluctuations related to the OCT-A instrument in the literature. For example, Al-Sheikh et al.[37] have found a mean difference in VD between sessions: –0.3 (95% confidence interval [CI], 3.3 to –3.9) for the SCP and –0.1 (95% CI, 2.6 to –2.5) for the DCP with a high intraclass coefficient ratio (ICC = 0.90, $P = 0.33$ for the SCP; and 0.8, $P = 0.589$ for the DCP). At the level of DCP, the VD and FAZ area were stable. Furthermore, a significant correlation was found between VD at the level of SCP and SBP, at rest and after exercise.

**Table 3.** Variations of FAZ Area After Exercise in the Superficial and Deep Plexa in the Overall Study Population: Estimated Mean Change and Its 95% CI

| FAZ Area in % | Before Exercise | After 20 Minutes of Exercise | *P* |
|---|---|---|---|
| Superficial plexus | 0.29 | 0.28 | 0.98 |
| | 95% CI (0.26–0.31) | 95% CI (0.25–0.31) | |
| Deep plexus | 0.35 | 0.37 | 0.3 |
| | 95% CI (0.32–0.38) | 95% CI (0.35–0.4) | |

Our results are consistent with those of Alnawaiseh et al.,[38] who have described a significant decrease in peripapillary and parafoveal VD after exercise as well. They also have found a significant correlation between retinal VD and SBP.

The decrease of VD at the level of the SCP with exercise could be related to an increase of intraocular pressure (IOP). In an animal trial, a progressive decrease in the blood flow velocity occurred as the IOP was raised during exercise, with a theoretical no-flow point in the retinal arteries estimated to be approximately 8 mm Hg. Before this end point, the retinal flow would be maintained by arterial vasodilatation.[39] This last result has been confirmed by another study with anesthetized rats, where retinal capillary density and retinal blood flow decreased with acute induced IOP elevation, especially as the mean arterial pressure was low.[40]

In contrast, some studies[41] have found that the IOP decreases after exercise, with no significant difference on the retinal blood flow. The mechanism maintaining a constant retinal blood flow might be due to a consecutive retinal arterial vasoconstriction.[42,43]

The second hypothesis suggests a physiological vascular redistribution in favor of the skeletal muscles. This last hypothesis is also supported by the fact that ocular perfusion pressure tends to decrease at the end of exercise.[44] A contradictory study[45] has assessed that mean flow velocity and resistive indices are stabilized in the central retinal artery, unlike in the ophthalmic artery, suggesting a retinal autoregulation system.

Interestingly, our results showed a statistically significant increase of FD at the level of the DCP after physical exercise, which could reflect a vascular recruitment in this area (vasodilatation of arterioles) and thus an increase in complexity

**Table 2.** Repeatability of Measurements of Vascular Density With OCT-Angiography at the Level of Superficial Capillary Plexus, Using a Bland-Altman Plot

| | 1–2 | | | 1–3 | | | 2–3 | | |
|---|---|---|---|---|---|---|---|---|---|
| **Agreement Between Measures** | **ICC** | **95% CI** | **CR** | **ICC** | **95% CI** | **CR** | **ICC** | **95% CI** | **CR** |
| Whole SCP before exercise | 0.96 | 0.94–0.97 | 1.46 | 0.51 | 0.34–0.69 | 1.73 | 0.97 | 0.96–0.98 | 1.2 |
| Whole SCP after exercise | 0.88 | 0.82–0.93 | 2.76 | 0.89 | 0.84–0.94 | 2.56 | 0.98 | 0.97–0.99 | 1.01 |
| Parafoveal SCP before exercise | 0.88 | 0.83–0.93 | 2.93 | 0.90 | 0.85–0.95 | 2.64 | 0.96 | 0.95–0.98 | 1.53 |
| Parafoveal SCP after exercise | 0.95 | 0.93–0.97 | 1.77 | 0.96 | 0.95–0.98 | 1.47 | 0.95 | 0.94–0.97 | 1.62 |

For ICC and its 95% CI: the higher the ratio, the better the repeatability. Strength of agreement beyond chance is fair between 0 and 0.25, moderate between 0.26 and 0.50, substantial between 0.51 and 0.75, and almost perfect between 0.76 and 1.00. For CR: the lower the coefficient, the smaller the deviation of the mean. Columns 1–2, 1–3, and 2–3 assess the agreement between measures 1 and 2, 1 and 3, and 2 and 3, respectively.

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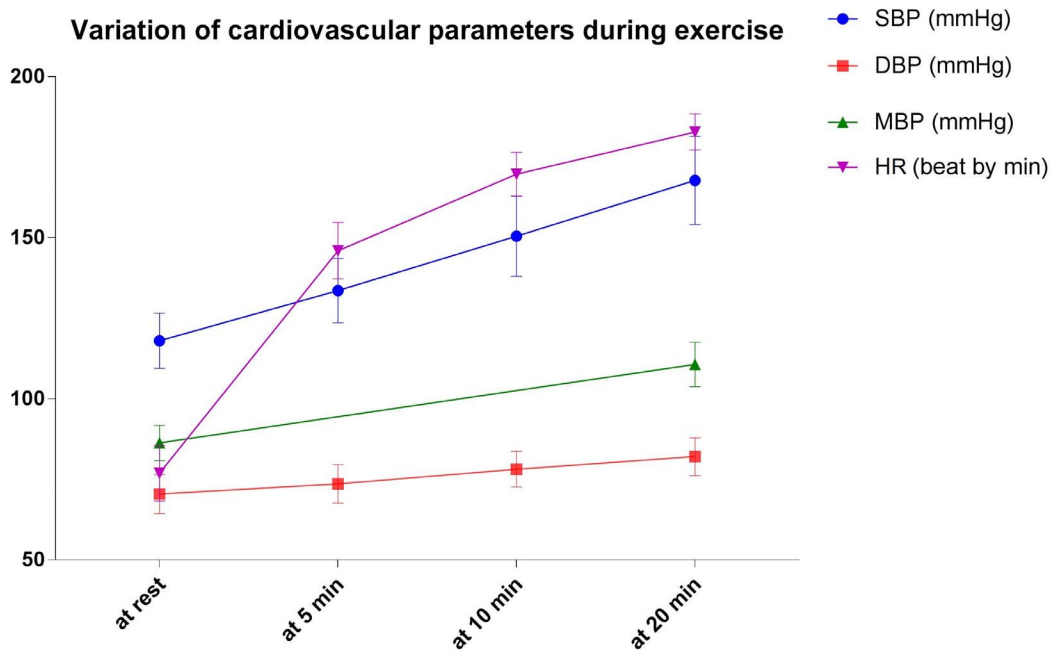


**Figure 2.** Variations of cardiovascular parameters during exercise in the study population. HR, heart rate; MBP, mean calculated blood pressure.

at the level of this capillary plexus consequent to physical effort. By comparison, a significant decrease of FD in OCT-A has been identified in aging groups[25] or in diabetic retinopathy.[29,31] Among symptoms reported by many healthy people during an intense physical effort, blurred vision has been mentioned.[46–48] The potential hypotheses are metabolic causes, such as hypotension, dehydration, low level of blood sugar following exercise, or local causes like dry eye because of windy or hot weather. One might ask whether blurred vision after exercise can be at least partly explained by the decreased retinal VD in the SCP on OCT-A. Our study population was asymptomatic but displayed a decrease of retinal VD. However, older age groups with cardiovascular disease could display a more severe drop in VD during/immediately after physical exercise.

In spite of its prospective character, our study had several limitations. First of all, our cohort was small and there was no older age group among included patients. A standardized bicycle ergonometer was not used. The study protocol was built to more closely resemble the cardiologic stress protocol. Twenty minutes seems to be the ideal duration for exercise. Shorter duration does not guarantee the most efficient implementation possible of the cardiovascular system, so retinal vascular changes may not be observed.

**Table 4.** Variations of Fractal Dimension After Exercise in the Superficial and Deep Plexa in the Overall Study Population: Estimated Mean Change and Its 95% CI

| Overall Population | Before Exercise | After 20 Minutes of Exercise | *P* |
|---|---|---|---|
| Fractal dimension at the superficial plexus | 1.63 | 1.63 ± 0.11 | 0.33 |
| Fractal dimension at the deep plexus | 1.68 | 1.69 | **<0.0001** |

Bold values indicate statistical significance $P < 0.05$.

It might be interesting to know if retinal VD in OCT-A would be modified in the same way in older people, who are at higher risk of cardiovascular disease. As physical effort in older people—with more risk of atheromatic diseases—must be approved and monitored by the cardiologist, we did not include this part of the population in our study. Furthermore, the present protocol could be applied to diabetic or retinal vein occlusion patients, in order to assess the exercise-induced vascular changes and thus the ischemic potential in both eyes. A joint study involving cardiologists and ophthalmologists would be interesting for exploring the potential retinal ischemic risk in older people, as described for heart and lower-limb vessels.

In conclusion, OCT-A provides reliable, noninvasive, qualitative and quantitative information of retinal vasculature and FAZ area. Our study supports the hypothesis of a retinal autoregulation system.[46] A rest period might be recommended before OCT-A data acquisition, as modifications of cardiovascular parameters could distort retinal vascular data. These exercise-induced variations would imply an essential normalization of OCT-A examination.

**Table 5.** Pearson Correlation Between the Variations of the Vascular Density at the Level of Superficial and Deep Plexa in the Overall Study Population: Estimated Mean Change and Its 95% CI

| Vascular Density at the SCP | SBP at Rest | | SBP After Exercise | | Variations of SBP (After-Before Exercise) | |
|---|---|---|---|---|---|---|
| | Coeff | *P* | Coeff | *P* | Coeff | *P* |
| Whole | **−0.72** | **<0.0001** | **−0.78** | **<0.0001** | **−0.74** | **<0.0001** |
| Fovea | −0.14 | 0.24 | −0.008 | 0.94 | −0.24 | 0.05 |
| Parafovea | **−0.65** | **<0.0001** | **−0.72** | **<0.0001** | **−0.66** | **<0.0001** |

Bold values indicate statistical significance $P < 0.05$. Coeff, coefficient.

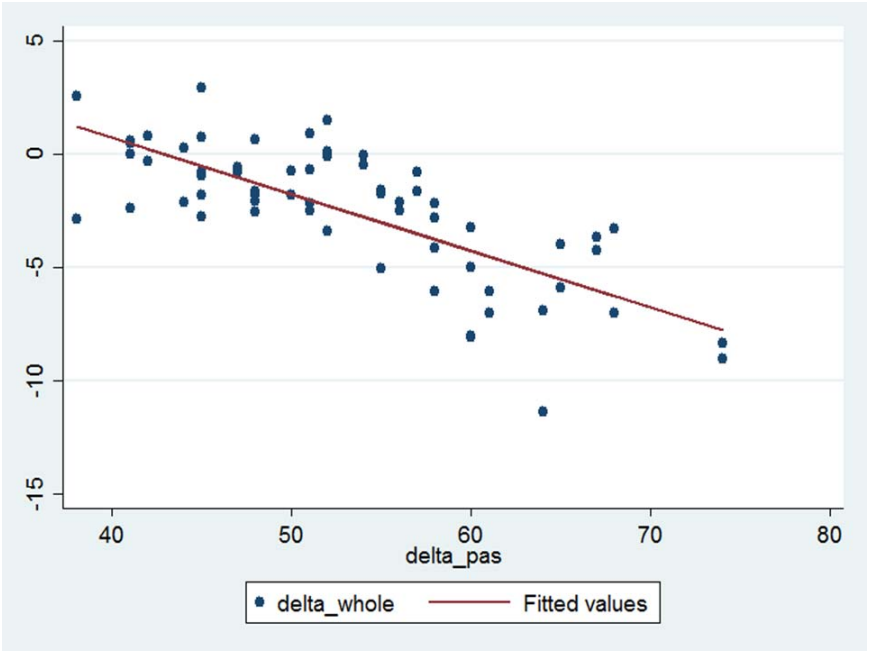


FIGURE 3. Linear distribution of vascular density at the level of the whole SCP as a function of variation. The *x*-axis represents variations of the vascular density at the whole SCP; *y*-axis represents the variations of the systolic blood pressure over the exercise. The *red line* shows the best fit linear regression.

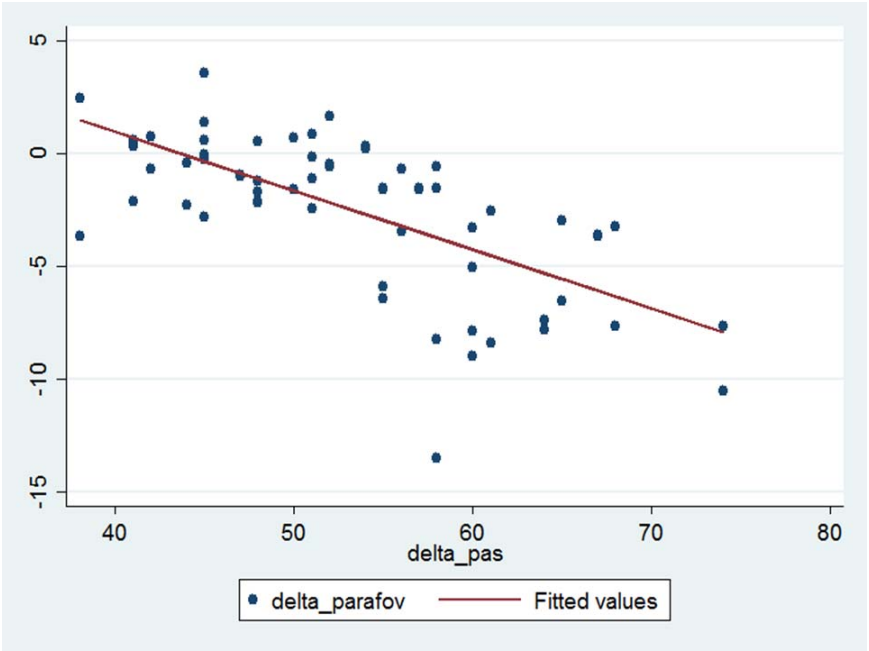


FIGURE 4. Linear distribution of vascular density at the level of the parafoveal SCP as a function of SBP variation. The *x*-axis represents variations of the vascular density at the parafoveal SCP; *y*-axis represents the variations of the systolic blood pressure during the exercise. The *red line* shows the best fit linear regression.

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## *References*

1. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128:873–934.

2. Rivera-Brown AM, Frontera WR. Principles of exercise physiology: responses to acute exercise and long-term adaptations to training. *PM R*. 2012;4:797–804.
3. Carter JB, Banister EW, Blaber AP. Effect of endurance exercise on autonomic control of heart rate. *Sports Med Auckl NZ*. 2003;33:33–46.
4. Maiorana A, O'Driscoll G, Taylor R, Green D. Exercise and the nitric oxide vasodilator system. *Sports Med Auckl NZ*. 2003; 33:1013–1035.
5. Cocks M, Wagenmakers AJM. The effect of different training modes on skeletal muscle microvascular density and endothelial enzymes controlling NO availability. *J Physiol*. 2016; 594:2245–2257.
6. Durand MJ, Dharmashankar K, Bian J-T, et al. Acute exertion elicits a H2O2-dependent vasodilator mechanism in the microvasculature of exercise-trained but not sedentary adults. *Hypertension*. 2015;65:140–145.
7. Robinson AT, Fancher IS, Mahmoud AM, Phillips SA. Microvascular vasodilator plasticity after acute exercise. *Exerc Sport Sci Rev*. 2018;46:48–55.
8. Coscas F, Sellam A, Glacet-Bernard A, et al. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57:OCT211-OCT223.
9. Iafe NA, Phasukkijwatana N, Chen X, Sarraf D. Retinal capillary density and foveal avascular zone area are age-dependent: quantitative analysis using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016; 57:5780–5787.
10. Ting DSW, Tan GSW, Agrawal R, et al. Optical coherence tomographic angiography in type 2 diabetes and diabetic retinopathy. *JAMA Ophthalmol*. 2017;135:306–312.
11. Santos AR, Alves D, Santos T, Figueira J, Silva R, Cunha-Vaz JG. Measurements of retinal fluid by OCT leakage in diabetic macular edema: a biomarker of visual acuity response to treatment. *Retina*. 2017;39:52–60.
12. Moein H-R, Novais EA, Rebhun CB, et al. Optical coherence tomography angiography to detect macular capillary ischemia in patients with inner retinal changes after resolved diabetic macular edema. *Retina*. 2017;38:2277–2284.
13. Iida Y, Muraoka Y, Ooto S, et al. Morphologic and functional retinal vessel changes in branch retinal vein occlusion: an optical coherence tomography angiography study. *Am J Ophthalmol*. 2017;182:168–179.
14. Seknazi D, Coscas F, Sellam A, et al. Optical coherence tomography angiography in retinal vein occlusion: correlations between macular vascular density, visual acuity, and peripheral nonperfusion area on fluorescein angiography. *Retina*. 2017;38:1562–1570.
15. Amoroso F, Miere A, Semoun O, Jung C, Capuano V, Souied EH. Optical coherence tomography angiography reproducibility of lesion size measurements in neovascular age-related macular degeneration (AMD). *Br J Ophthalmol*. 2017;102: 821–826.
16. Al-Sheikh M, Iafe NA, Phasukkijwatana N, Sadda SR, Sarraf D. Biomarkers of neovascular activity in age-related macular degeneration using OCT angiography. *Retina*. 2017;38:220–230.
17. Ahmed D, Stattin M, Graf A, et al. Detection of treatment-naive choroidal neovascularization in age-related macular degeneration by swept source optical coherence tomography angiography. *Retina*. 2017;38:2143–2149.
18. Eandi CM, Ciardella A, Parravano M, et al. Indocyanine green angiography and optical coherence tomography angiography of choroidal neovascularization in age-related macular degeneration. *Invest Ophthalmol Vis Sci*. 2017;58:3690–3696.
19. Snodderly DM, Weinhaus RS, Choi JC. Neural-vascular relationships in central retina of macaque monkeys (Macaca fascicularis). *J Neurosci*. 1992;12:1169–1193.
20. Delaey C, van de Voorde J. Regulatory mechanisms in the retinal and choroidal circulation. *Ophthalmic Res*. 2000;32:249–256.
21. Pournaras CJ, Rungger-Brändle E, Riva CE, Hardarson SH, Stefansson E. Regulation of retinal blood flow in health and disease. *Prog Retin Eye Res*. 2008;27:284–330.
22. Glenny RW, Robertson HT, Yamashiro S, Bassingthwaighte JB. Applications of fractal analysis to physiology. *J Appl Physiol (1985)*. 1991;70:2351–2367.
23. Daxer A. Fractals and retinal vessels. *Lancet*. 1992;339:618.
24. Family F, Masters BR, Platt DE. Fractal pattern formation in human retinal vessels. *Phys Nonlinear Phenom*. 1989;38:98–103.
25. Azemin MZC, Kumar DK, Wong TY, et al. Age-related rarefaction in the fractal dimension of retinal vessel. *Neurobiol Aging*. 2012;33:194.
26. Stosic T, Stosic BD. Multifractal analysis of human retinal vessels. *IEEE Trans Med Imaging*. 2006;25:1101–1107.
27. Mainster MA. The fractal properties of retinal vessels: embryological and clinical implications. *Eye (Lond)*. 1990;4: 235–241.
28. Avakian A, Kalina RE, Sage EH, et al. Fractal analysis of region-based vascular change in the normal and non-proliferative diabetic retina. *Curr Eye Res*. 2002;24:274–280.
29. Zahid S, Dolz-Marco R, Freund KB, et al. Fractal dimensional analysis of optical coherence tomography angiography in eyes with diabetic retinopathy. *Invest Ophthalmol Vis Sci*. 2016; 57:4940–4947.
30. Chen Q, Ma Q, Wu C, et al. Macular vascular fractal dimension in the deep capillary layer as an early indicator of microvascular loss for retinopathy in type 2 diabetic patients. *Invest Ophthalmol Vis Sci*. 2017;58:3785–3794.
31. Chen Q, Ma Q, Wu C, et al. Macular vascular fractal dimension in the deep capillary layer as an early indicator of microvascular loss for retinopathy in type 2 diabetic patients. *Invest Ophthalmol Vis Sci*. 2017;58:3785–3794.
32. Carta P, Aru G, Barbieri MT, Mele M. Bicycle ergometry exercise tests: a comparison between 3 protocols with an increasing load [in Italian]. *Med Lav*. 1991;82:56–64.
33. Riboli A, Cè E, Rampichini S, et al. Comparison between continuous and discontinuous incremental treadmill test to assess velocity at V̇O2max. *J Sports Med Phys Fitness*. 2017; 57:1119–1125.
34. Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whipp BJ. Optimizing the exercise protocol for cardiopulmonary assessment. *J Appl Physiol*. 1983;55:1558–1564.
35. Fletcher GF, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards: a statement for health professionals from the American Heart Association. *Circulation*. 1990;82: 2286–2322.
36. Messaï E, Claude S-M. *Guide Des Chiffres et Formules Utiles en Pratique Médicale*. Paris: Arnette Blackwell; 1995.
37. Al-Sheikh M, Tepelus TC, Nazikyan T, Sadda SR. Repeatability of automated vessel density measurements using optical coherence tomography angiography. *Br J Ophthalmol*. 2017;101:449–452.
38. Alnawaiseh M, Lahme L, Treder M, Rosentreter A, Eter N. Short-term effects of exercise on optic nerve and macular perfusion measured by optical coherence tomography angiography. *Retina*. 2017;37:1642–1646.
39. Ffytche TJ, Bulpitt CJ, Kohner EM, Archer D, Dollery CT. Effect of changes in intraocular pressure on the retinal microcirculation. *Br J Ophthalmol*. 1974;58:514–522.
40. Zhi Z, Cepurna W, Johnson E, Jayaram H, Morrison J, Wang RK. Evaluation of the effect of elevated intraocular pressure


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and reduced ocular perfusion pressure on retinal capillary bed filling and total retinal blood flow in rats by OMAG/OCT. *Microvasc Res*. 2015;101:86–95.

41. Iester M, Torre PG, Bricola G, Bagnis A, Calabria G. Retinal blood flow autoregulation after dynamic exercise in healthy young subjects. *Ophthalmologica*. 2007;221:180–185.
42. Harris A, Arend O, Bohnke K, Kroepfl E, Danis R, Martin B. Retinal blood flow during dynamic exercise. *Graefes Arch Clin Exp Ophthalmol*. 1996;234:440–444.
43. Kergoat H, Lovasik JV. Response of parapapillary retinal vessels to exercise. *Optom Vis Sci*. 1995;72:249–257.
44. Lovasik JV, Kergoat H, Riva CE, Petrig BL, Geiser M. Choroidal blood flow during exercise-induced changes in the ocular perfusion pressure. *Invest Ophthalmol Vis Sci*. 2003;44:2126–2132.
45. Németh J, Knézy K, Tapasztó B, Kovács R, Harkányi Z. Different autoregulation response to dynamic exercise in ophthalmic and central retinal arteries: a color Doppler study in healthy subjects. *Graefes Arch Clin Exp Ophthalmol*. 2002;240:835–840.
46. Croswell J. Blurry Vision During Exercise. Available at: https://www.livestrong.com/article/482531-blurry-vision-during-exercise/. Accessed March 4, 2018.
47. Niedziocha L. Signs & Symptoms: Dizziness & Loss of Vision During & After Exercise. Available at: https://www.livestrong.com/article/477838-signs-symptoms-dizziness-loss-of-vision-during-after-exercise/. Accessed March 4, 2018.
48. Shape Magazine. Do You Ever Get Dizzy When You Work Out? Available at: https://www.shape.com/fitness/tips/why-you-get-dizzy-when-you-work-out. Accessed March 4, 2018.

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