

Choroidal Structural Changes in Smokers Measured Using Choroidal Vascularity Index

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PURPOSE. Cigarette smoking is a known risk factor for vascular dysfunction. This study evaluated choroidal structural changes in smokers using the choroidal vascularity index (CVI) derived from image binarization on spectral domain optical coherence tomography scans with enhanced depth imaging (EDI-OCT).

METHODS. This cross-sectional study included 39 smokers and 44 non-smokers. Choroidal images on EDI-OCT were binarized into luminal area (LA) and stromal area (LA). CVI was calculated as the ratio of LA to total choroid area (TCA). CVI, foveal retinal thickness (FRT), and subfoveal choroidal thickness (SFCT) between smokers and non-smokers were compared using likelihood ratio test with linear mixed model. Trend and subgroup analysis were performed to investigate the dose-dependent relationship between CVI/FRT/SFCT and pack-years.

RESULTS. CVI in smokers ($65 \pm 2\%$) was lower compared to non-smokers ($67 \pm 2\%$, $P = 0.0001$). The difference remained significant after adjusting for age ($P = 0.001$). There was no significant association between cigarette smoking and FRT/SFCT. CVI decreased by 0.12% with each unit increase in smoking measured by pack-year ($P = 0.0009$). In subgroup analysis, those who smoked 8 to 12 and >12 pack-years had significantly lower CVI compared to non-smokers (both $P < 0.05$).

CONCLUSIONS. Cigarette smoking is associated with decreased choroidal vascularity in healthy subjects, and this association appears to be dose dependent. CVI might be a non-invasive marker of vascular health in smokers.

Keywords: choroidal vascularity index, choroid, smoking, cigarette smoking, vascular dysfunction

Cigarette smoking is one of the leading causes for preventable illness and death worldwide.¹ It is responsible for substantial morbidities and mortalities as well as enormous economic cost, totaling more than \$1.4 trillion USD in health care costs and lost productivity.²

Cigarette smoke contained more than 4000 different constituents, many of which had toxic and carcinogenic properties.³ Among many of its adverse effects to the human body, cigarette smoking was a known risk factor for systemic vascular dysfunction. WHO has estimated that smoking is responsible for 10% of all cardiovascular deaths in the world.⁴ The total disease burden attributable to cigarette smoking and secondhand smoke was approximated 6.3 million deaths annually, one third of which were secondary to cardiovascular disease.⁵ To eye-health care providers, smoking is strongly associated with common sight-threatening conditions, such as age-related macular degeneration, diabetic retinopathy, cataract, contact lens-related keratitis and Graves' ophthalmopathy.^{6,7}

Choroid is the vascular layer of the eye. Recent advancement of optical coherence tomography (OCT) technology, especially with enhanced depth imaging (EDI), has allowed for fast, non-invasive, and detailed assessment of choroidal

structure.⁸ Knowledge of choroidal structural change may in turn allow clinicians and scientists to gain insight into systemic vascular health status.⁹

Previously, choroidal thickness (CT) was used as the main surrogate marker for choroidal structure. However, the effect of cigarette smoking on CT has been inconsistent.¹⁰⁻¹⁴ Recently, choroidal vascularity index (CVI) was proposed as a novel and robust tool to evaluate choroidal vasculature in both healthy and diseased eyes.^{15,16} In this study, we have compared choroidal structural change between healthy smokers and non-smokers using CVI.

METHODS

In this cross-sectional study, subjects were recruited from March 2017 to April 2018 (14 months) at a tertiary referral eye care center in India. Ethical approval was obtained from the Institutional Review Board and informed consent was obtained from each subject. This study adhered to the tenets of the Declaration of Helsinki. Subjects with any systemic or ocular diseases were excluded. Demographic data and history of



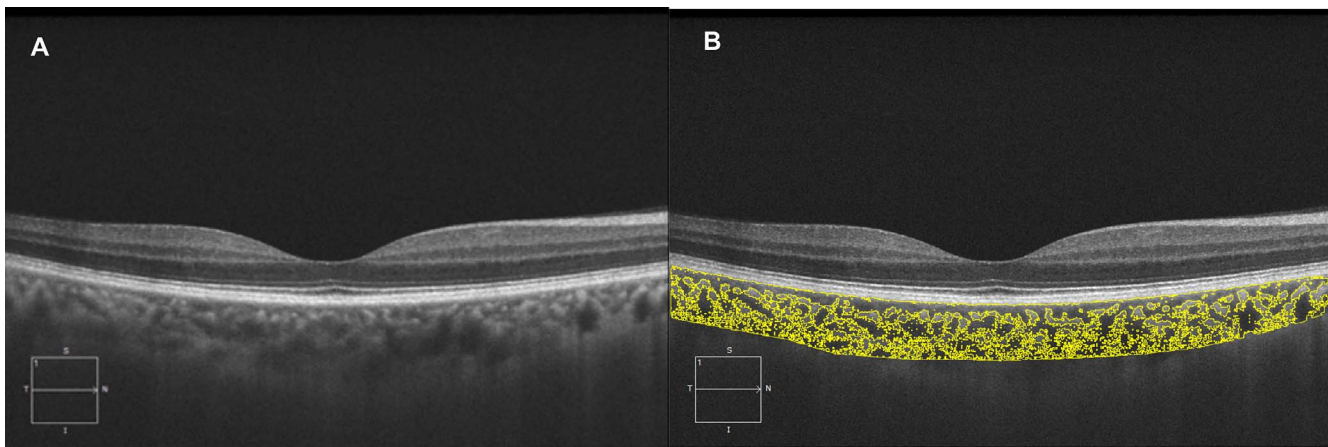


FIGURE 1. Image binarization for choroid in a healthy smoker. (A) Original OCT image from Zeiss HD OCT 5000 demonstrating choroid in the subfoveal scan. (B) Segmentation and binarization of the entire subfoveal choroidal area using modified image binarization approach and *overlay* of region of interest created after binarization was performed on the OCT image.

cigarette smoking, including duration and amount, were collected.

Image Acquisition and Analysis

All subjects underwent spectral domain OCT with EDI using standardized protocol (Zeiss Cirrus HD OCT 5000). The macular region was scanned using a 7 horizontal line scan ($30^\circ \times 5^\circ$) centered on the fovea, with 100 frames averaged in each B-scan. The raster scan passing through the fovea was selected for analysis. Choroidal scleral interface was defined as a clear hyper-reflective band outer to the vascular structure of the choroid. All the measurements (CT and FRT) were done manually by a single grader using calipers provided in the software embedded in the machine. It was a single point measurement at the deepest point of the fovea. For the measurement of CVI, image binarization was carried out using methods proposed by Sonoda et al.¹⁷ with modifications as previously described¹⁵ (Fig. 1). In brief, open source ImageJ software was used for image processing¹⁸ (version 1.47; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA; <http://imagej.nih.gov/ij/>). The OCT B scan (Fig. 1A) was first converted to 8-bit images using default setting. Subsequently, Niblack's auto local threshold tool was applied to allow demarcation of luminal area (LA) and stromal area (SA). Then total choroidal area (TCA) was selected using polygonal tool by manual plotting of the choroidal upper border marked at the retinal pigment epithelium (RPE) and the lower border marked at the choroid-sclera junction. The entire length of the OCT B-scan was used for analysis. The image was then converted back to an RGB (red, green, blue) image to allow computation of size of LA by the color threshold tool. Lastly, CVI was calculated as a proportion of LA to TCA (Fig. 1B).

Statistical Analysis

Age and cigarette smoking history were treated as independent variables, while CVI, FRT, and SFCT were treated as dependent variables. Amount of cigarette smoking was based on total exposure measured by pack-years, which was the number of years of smoking multiplied by the number of packs of cigarettes smoked per day. This was zero for non-smokers.

The measurement of dependent variables on both eyes from the same subject were regarded as non-independent, repeat observations. To account for this, linear mixed model was used

with age and cigarette smoking as fixed factors and subject as a random factor. Thus, the resulting mixed model to explore the effect of these factors on the dependent variables (Y) was:

$$Y \sim \text{age} + \text{smoking} + (1|\text{SubjectID}) + \varepsilon$$

The term $(1|\text{SubjectID})$ refers to random effect, which is an R-typical notation format, indicating that the intercept is different for each patient. The error term ε represents the deviations from the predictions due to factors that are beyond reach of fixed and random components.

The effect of each fixed factor on the dependent variables was evaluated for statistical significance by comparing the full model with the reduced model (i.e., using Likelihood Ratio tests). The analysis was performed using R (R Core Team 2012) and with lme4 package.

Trend analysis between structural parameter (CVI/FRT/SFCT) and unit increase in smoking (pack-year) was performed with linear mixed model to account for measurements from both eyes of the same subject and adjusted for age. A P value of <0.05 was considered statistically significant.

RESULTS

A total of 39 smokers and 44 non-smokers were included in this study (Table 1). The mean age was $41.79 (\pm 6.48)$ years for smokers and $36.56 (\pm 8.77)$ years for non-smokers. Smokers included in this study were significantly older than non-smokers ($P < 0.0001$). All subjects were male gender. The average amount of cigarette smoking was $8.89 (\pm 5.33)$ pack-years.

Mean CVI among smokers was $65 \pm 2\%$, and this was lower compared to CVI in non-smokers ($67 \pm 2\%$, $P = 0.0001$; Table 1). The difference remained significant after adjusting for age ($P = 0.001$). There was no significant difference in FRT/SFCT between smokers and non-smokers.

In trend analysis, CVI decreased by 0.12% with each unit increase in smoking measured by pack-year, and this was statistically significant ($P = 0.0009$; Table 2). Changes in FRT or SFCT with increasing pack-year were not significant. In subgroup analysis (Fig. 2; Table 2), those who smoked 8 to 12 and >12 pack-years showed significant reduction in CVI compared to non-smokers, while those smoked ≤ 8 pack-years did not. There was no significant difference in FRT/SFCT in smoking subgroups except those who smoked 8 to 12 pack-years had higher FRT compared to non-smokers.

TABLE 1. Descriptive Statistics for Baseline Characteristics of Study Subjects

Parameter	Smoker	Non-Smoker	P Value†	Adjusted P Value‡
Number of patients [No. (%)]	39 (46.9)	44 (53.1)	-	-
Number of eyes [No. (%)]	78 (46.9)	88 (53.1)	-	-
Age in years [y, Mean ± SD]	41.79 ± 6.48	36.56 ± 8.77	<0.0001	-
Pack years [Mean ± SD]	8.89 ± 5.33	-	-	-
CVI [Mean ± SD]	0.65 ± 0.02	0.67 ± 0.02	0.0001	0.001
FRT [μm, Mean ± SD]	223.56 ± 22.18	220.92 ± 17.56	0.4001	0.402
SFCT [μm, Mean ± SD]	304.25 ± 57.09	311.35 ± 68.89	0.4692	0.570

† Obtained using *t*-test for independent samples.

‡ Obtained using linear mixed model to account for both eyes from the same patient and adjusted for age.

DISCUSSION

In this study, we have shown that cigarette smoking had a dose-dependent association with reduction of CVI in male smokers free of any systemic or ocular diseases. There was no significant association between cigarette smoking and FRT or SFCT.

Several pathogenic mechanisms linking cigarette smoking to systemic vascular dysfunction have been demonstrated in the literature. Firstly, components in cigarette smoke, particularly nicotine, was associated with a direct toxic effect to endothelium, resulting in its structural damage both in vitro and in vivo.^{19,20} Secondly, smoking was shown to interfere with normal vascular physiology. Flow-mediated vasodilatation in brachial and coronary arteries was reported to be impaired by smoking.^{21,22} Thirdly, smoking was associated with a change in serum lipid profiles in a proatherogenic manner.^{23,24} Lastly, cigarette smoking was linked to inflammation, which was tightly correlated with formation of atherosclerotic plaques.²⁵ This was supported by the findings of elevated white blood cell counts and proinflammatory cytokines in smokers.²⁵⁻²⁸

The choroid is the vascular layer of the eye. It has the highest blood flow per unit weight of all tissues in the body.²⁹ Many systemic physiological and pathological conditions that affect hemodynamics are shown to have an impact on choroidal structure and function.⁹ The effect of smoking on the choroid has been studied previously. Using Wistar rat as an animal model, the index of choroidal vascular resistance—defined as systolic tail arterial pressure/choroidal blood flow—increased significantly after inhalation of smoke for 25 weeks. However, there were no histopathological abnormalities detected in the choroid.³⁰ Looking at the acute effects of smoking on ocular hemodynamics with the laser speckle method, cigarette smoking increased blood velocity in the choroid-retina in habitual smokers within 30 minutes after smoking.³¹

Using OCT technology, we investigated the effect of smoking on choroidal thickness. However, the results were inconsistent. In the assessment of the acute effect of smoking, Sizmaz et al. showed cigarette smoking caused a significant decrease in CT 1 and 3 hours after smoking,¹⁰ while Ulas et al. reported a significant increase in CT within 1 hour of smoking that subsequently returned to baseline.¹¹ Regarding chronic effects of smoking, decreased CT were more often observed in chronic smokers.^{12,14} However, there was one report that showed no significant difference in CT between smokers and non-smokers.¹³ This discrepancy can also be due to the fact that CT being a single dimension measurement may result in possible inherent variability.

Choroid is a heterogeneous tissue consisting of blood vessels and stroma including connective tissue, nerves, extracellular fluid, and melanocytes. Measurement of CVI takes into account both the vascular and interstitial components of the choroid. Therefore, CVI might be a more robust marker than CT. Indeed, in a large cohort of healthy subjects, CVI (but not CT) was shown to be independent from ocular and systemic factors such as axial length, intraocular pressure, age, and systolic blood pressure.¹⁶ The utility of CVI to evaluate choroidal vasculature was also validated in common ocular and systemic diseases.^{15,32-38} In this study, cigarette smoking was shown to be associated with decreased CVI and not CT. This effect may arise from decreased LA or increased SA or a combination of both in chronic smokers. The exact mechanism was not explored in the current study, but a plausible hypothesis could be extrapolated from how cigarette smoking affects blood vessels elsewhere in the body. Decreased LA could be a result of impaired vasodilatation secondary to endothelial dysfunction, whereas increased SA might be due to a chronic proinflammatory response leading to exudation and fibrosis. In addition, CVI is a two-dimensional measurement and can provide more robustness and stability to the measurement as against CT, which is a single-dimensional measurement. Further studies would be required to test these hypotheses.

TABLE 2. Trend Analysis and Subgroup Analysis for Smoking and Choroidal/Retinal Structural Parameters

Group	No.	CVI			SFCT (μm)			FRT (μm)		
		Mean ± SD	β	P Value	Mean ± SD	β	P Value	Mean ± SD	β	P Value
Non-smoker	44	0.668 ± 0.021	-	Ref	311.35 ± 68.85	-	Ref	220.92 ± 17.56	-	Ref
Smoker*	39	0.655 ± 0.021	-0.001	<0.001†	304.25 ± 57.09	-1.033	0.177†	223.56 ± 22.18	0.215	0.617†
Pack-year (≤4)#	10	0.659 ± 0.026	-0.011	0.082‡	308.25 ± 44.91	-3.018	0.882‡	219.70 ± 18.56	-0.202	0.974‡
Pack-year (4-8)#	11	0.658 ± 0.019	-0.009	0.139‡	296.36 ± 66.17	-15.72	0.424‡	219.18 ± 30.87	-0.944	0.876‡
Pack-year (8-12)#	9	0.649 ± 0.022	-0.019	0.009‡	330.72 ± 59.53	18.91	0.376‡	235.11 ± 17.09	15.42	0.021‡
Pack-year (>12)#	9	0.651 ± 0.015	-0.017	0.018‡	283.00 ± 47.31	-27.59	0.198‡	221.67 ± 13.68	0.697	0.915‡

* Trend analysis; # subgroup analysis.

† Obtained with pack-year as continuous variable.

‡ Obtained with four subgroups as categorical variable.

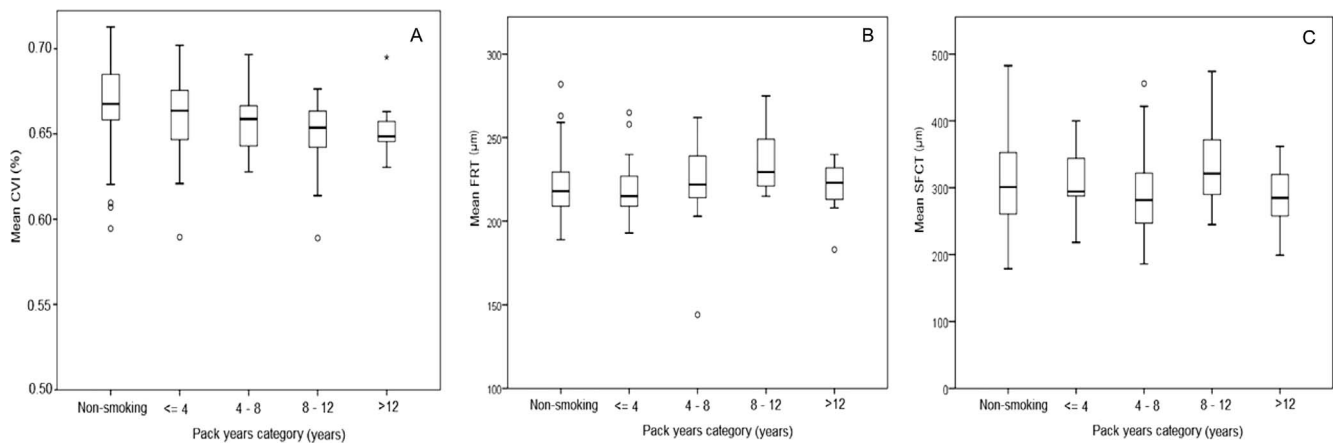


FIGURE 2. Box plots demonstrating the change in choroidal vasculature index (CVI) with increasing cigarette consumption (A), change in foveal retinal thickness (FRT) with increasing cigarette consumption (B), and change in subfoveal choroidal thickness (SFCT) with increasing cigarette consumption (C).

In our study, there was no significant difference in retinal thickness at the fovea between smokers and the control group. This result was consistent with previous reports in which smoking did not appear to affect retinal thickness in the healthy population,^{11,13,14} although certain layers within the retina could be thinner in smokers, such as the ganglion cell complex layer¹⁴ and retinal nerve fiber layer.³⁹ Interestingly, in our subgroup analysis, those who smoked 8 to 12 pack-years had higher FRT compared to controls. This difference could be real or a chance occurrence without true correlation, considering the fact that this was a posthoc subgroup analysis and that those with higher or lower cigarette exposure did not show any association. Future studies with larger sample size would be needed to validate this observation.

There are several limitations of this study. First, all participants were male. It was not clear whether similar changes could be observed in female smokers. Second, the average age of smokers was approximately 5 years older than that of non-smokers. However, this was accounted for with linear mixed model in data analysis. Third, due to the cross-sectional nature of this study, we were unable to establish a causal relationship between cigarette smoking and reduced CVI. Fourth, the sample size in our study is relatively small. It may not be powered to detect a difference in FRT and SFCT between smokers and non-smokers; however, we were able to demonstrate a significant relationship between CVI and smoking. The posthoc analysis between CVI and smoking stratified by cigarette exposure is also limited by a small sample size. Lastly, cigarettes consumed by subjects in this study included commercially available cigarettes containing tobacco, excluding other forms, such as cigars and herbal or menthol cigarette. Inability to control the brand of cigarettes that may have different composition was a limitation of our study.

In conclusion, cigarette smoking was shown to be associated with lower choroidal vasculature measured by CVI in a dose dependent manner. The utility of CVI as a non-invasive marker to predict systemic vascular dysfunction or onset of ocular diseases, such as age-related macular degeneration in smokers is worth exploring in future studies.

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