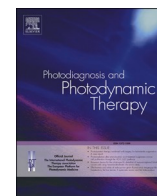




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## Early effects of inactivated (CoronaVac) SARS-CoV-2 vaccine on retrobulbar vascular blood flow and retinal vascular density

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### ABSTRACT

**Aims:** We aimed to investigate the early effects of inactivated SARS-CoV-2 vaccine on retrobulbar vascular blood flow and retinal vascular density in healthy subjects.

**Methods:** Thirty-four eyes of 34 healthy volunteers who received the CoronaVac (Sinovac Life Sciences, China) were included in this prospective study. Resistive index (RI), pulsatility index (PI) and peak systolic velocity (PSV) of the ophthalmic artery (OA), central retinal artery (CRA), and the temporal and nasal posterior ciliary arteries (PCA) were evaluated with color Doppler ultrasonography (CDUS) before vaccination, at the 2nd and 4th weeks after vaccination. Superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel density (VD), foveal avascular zone (FAZ), and choriocapillaris blood flow (CCF) measurements were made using optical coherence tomography angiography (OCTA).

**Results:** When compared to the pre-vaccination values, there was no significant change in OA-PSV, temporal-nasal PCA-PSV, CRA-EDV, temporal-nasal PCA-EDV at 2nd and 4th weeks after vaccination. However statistically significant reductions were found in the OA-RI, OA-PI, CRA-RI, CRA-PI, temporal-nasal PCA-RI, temporal-nasal PCA-PI values, CRA-PSV at post-vaccination 2nd week ( $p < 0.05$  for all). While there was sustained reduction in OA-RI, OA-PI, CRA-PSV, and nasal PCA-RI values at 4th week after vaccination, the change in CRA-RI, CRA-PI, temporal PCA-RI, temporal-nasal PCA-PI values were not significant compared to pre-vaccination values. There was no statistically significant difference in the SCP-VD, DCP-VD, FAZ and CCF measurements.

**Conclusions:** Our findings demonstrating that CoronaVac vaccine did not affect retinal vascular density in the early period, but it caused alterations in the retrobulbar blood flow.

### 1. Introduction

The coronavirus disease -COVID-19-, which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), resulted in an unprecedented pandemic worldwide. After a short while, several different types of vaccines have emerged to control the pandemic [1]. Although recent studies have shown acceptable efficacy, safety and tolerability of several COVID-19 vaccines, various adverse events have been reported

after vaccination [2].

Recently, numerous studies reported on potential adverse ocular posterior segment events following COVID-19 vaccination. [3] The most commonly reported retinal adverse events were acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM) [4]. Although the pathogenesis of AMN remains uncertain, a retinal microvascular etiology affecting the deep retinal capillary plexus (DCP) was proposed as the possible mechanism [5]. Furthermore, several

**Abbreviations:** AMN, acute macular neuroretinopathy; BCVA, best-corrected visual acuity; CCF, choriocapillaris blood flow; CDUS, color doppler ultrasonography; CRA, central retinal artery; DCP, deep retinal capillary plexus; FAZ, foveal avascular zone; IOP, intraocular pressure; MEWS, multiple evanescent white dot syndrome; OA, ophthalmic artery; OCTA, optical coherence tomography angiography; PAMM, paracentral acute middle maculopathy; PCA, posterior ciliary arteries; PI, pulsatility index; PSV, peak systolic velocity; RAO, retinal artery occlusion; RI, resistive index; RVO, retinal vein occlusion; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SCP, superficial capillary plexus.

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recent studies reported on ocular vascular events, such as central and branch retinal vein and retinal arterial occlusion, where possible hypercoagulable states following vaccination could be suspected. [6,7]

Color Doppler imaging (CDI) is a non-invasive diagnostic method for the evaluation of erythrocyte velocity in large ophthalmic vessels, which has long been used to assess retrobulbar hemodynamics in retinal diseases with good predictive value [8]. CDI is based on Doppler effect, which is the change in the frequency of sound reflected from movement of erythrocytes. This data is translated into a color using computer software, the red indicating movement toward the source, the blue movement away from the source. [9] The intensity of the color depends on the velocity of the moving particles. CDI can provide various velocity parameters of the ocular blood flow, such as peak systolic velocity (PSV) and end-diastolic velocity (EDV) in retrobulbar vessels. In addition, pulsatility index (PI) and the resistance index (RI) were calculated using CDI for the evaluation peripheral vascular resistance.

Optical coherence tomography angiography (OCTA) is another non-invasive tool allowing quantitative measurements of retina and choroid blood vessels, which is used for early detection of microvascular abnormalities caused by thromboembolic events, increased local ischemia or inflammation. [10] As a result, OCTA can quantitatively demonstrate retinal microvascular changes, making it a promising tool to evaluate COVID-related microvascular phenomenon. Based on the fact that the impaired vascular reactivity in retrobulbar vessels, and retinal microvasculature in several vascular-related ophthalmopathies, in this study, we aimed to investigate the effect of inactivated (CoronaVac) SARS-CoV-2 vaccine on retrobulbar blood flow parameters, retinal and choroidal vessel density through OCTA and color Doppler imaging.

## 2. Methods

### 2.1. Study design and patient population

In this prospective single center study, healthy volunteers without previous history of COVID-19 infection or vaccination, who received CoronaVac (Sinovac Life Sciences, China), were included. The study population was selected from COVID-19 naive healthy patients who had no symptoms suggestive of COVID infection before the study. In addition, absence of prior COVID-19 infection was confirmed using serum anti-SARS-CoV-2 IgGs. At each visit, oropharyngeal swabs were taken for SARS-CoV-genome and patients continued to the study if they have negative test results.

All patients underwent detailed ophthalmologic examination including best-corrected visual acuity assessment (BCVA), measurement of intraocular pressure (IOP), anterior segment evaluation with biomicroscopy and dilated fundus examination. Patients with any ocular and systemic disease, autoimmune disease, pregnancy, breastfeeding, migraine, active smokers, and medication usage were not enrolled into the study. In addition, patients with hyperrefractive errors (absolute spherical refractive error greater than 5 diopters and cylindrical refractive error more than 2 diopters) and BCVA less than 20/20 were not included. Only 1 eye was randomly selected for each participant and included into the analysis.

### 2.2. Procedural details

All patients underwent imaging with color Doppler ultrasonography (CDUS) and OCTA before vaccination, and at the 2nd and 4th weeks after vaccination. RI, PI and peak systolic velocity (PSV) of the ophthalmic artery (OA), central retinal artery (CRA), and the temporal posterior ciliary artery (PCA) and nasal PCA were evaluated with CDUS. Superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel density, foveal avascular zone (FAZ), and choriocapillaris blood flow (CCF) measurements were made with OCTA. To minimize the diurnal effect, all procedures were taken between 9 am and 12 am.

### 2.2.1. Optical coherence tomography angiography (OCTA)

OCTA images were obtained using RTVue-XR (Optovue, Angiovue, SD-OCT, Fremont, California USA) by the same trained operator with pupil dilation. Examinations with automatic scan quality values  $\geq 6$  were accepted for the analysis. Macular OCTA scans were performed using  $6 \times 6 \text{ mm}^2$  protocol. Automated default segmentation software automatically calculated the macular vessel densities in different retinal regions. Segmentation errors were checked by two experienced researchers and manually corrected if detected. Superficial capillary plexus (SCP) and deep capillary plexus (DCP) vessel density, foveal avascular zone (FAZ), and choriocapillaris blood flow (CCF) measurements were analyzed.

### 2.3. Color doppler ultrasonography

RI, PI and PSV of the OA, CRA), the temporal and nasal PCA were evaluated with CDUS. All CDUSs were performed by the same experienced radiologist using a 12–17 MHz linear probe with high-resolution scanner (Aplio 500, Toshiba systems, Tokyo, Japan). Examinations were performed in both eyes while the patients in supine position with closed eye, avoiding pressure on the globe as described before. [11] Blood flow velocities of the ophthalmic artery (OA), central retinal artery (CRA), and the temporal and nasal posterior ciliary arteries (PCA) were measured directly as previously described. [12] The RI and PI were calculated automatically by imaging device for each vessel studied.

The study adhered to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. Written informed consent was obtained from all subjects enrolled in the study.

### 2.4. Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 16 (SPSS Inc., Chicago, IL, USA). The normality of the data was confirmed using the Shapiro–Wilk Test and found not to be normally distributed. Hence, continuous variables were presented as medians and interquartile ranges (IQRs) throughout. Comparisons between the pre-vaccination values and post-vaccination 2nd and 4th week values were performed using the Wilcoxon signed rank test. Statistical significance was set as a p-value of  $<0.05$ .

## 3. Results

A total of 34 healthy volunteers were enrolled in the study (mean age of  $37 \pm 10$  years, 26 (76%) female). All subjects had single dose CoronaVac vaccine in the beginning of the study and all of them were followed for 4 weeks. None of the patients were excluded during the follow-up period. No ocular and systemic complications were observed during the study period.

### 3.1. CDUS findings

When compared to the pre-vaccination values, there was no significant change in OA-PSV, temporal-nasal PCA-PSV, CRA-EDV, and temporal-nasal PCA-EDV values at 2nd and 4th weeks after vaccination. On the other hand, statistically significant reductions were found in the OA-RI, OA-PI, CRA-RI, CRA-PI, temporal-nasal PCA-RI, temporal-nasal PCA-PI, CRA-PSV values at post-vaccination 2nd week ( $p < 0.05$ ). While there was sustained reduction in OA-RI, OA-PI, OA-EDV, CRA-PSV, and nasal PCA-RI values at the 4th week after vaccination, the change in CRA-RI, CRA-PI, temporal PCA-RI, temporal-nasal PCA-PI values were not significant compared to pre-vaccination values. In addition, OA-EDV showed a significant increase at post-vaccine 2nd and 4th week compared to pre-vaccine value. Pre-vaccine and post-vaccine 2nd and 4th week mean values of RI, PI and PSV measured in the OA, CRA, temporal and nasal PCA were shown in the [Table 1](#).

**Table 1**  
Doppler parameters of the ophthalmic artery, central retinal and posterior ciliary artery before and after vaccination.

	Before Vaccine	After 2 weeks	After 4 weeks	P value Pre-after 2 weeks Pre-after 4 weeks
<b>Ophthalmic artery</b>				
RI	0.68 (0.08)	0.66 (0.08)	0.64 (0.09)	<0.001 <0.001
PI	1.25 (0.49)	1.23 (0.33)	1.16 (0.36)	0.001 0.004
EDV (cm/s)	9.63 (3.50)	10.97 (5.96)	11.35 (4.14)	0.002 0.004
PSV (cm/s)	32.85 (11.35)	32.95 (14.7)	31.35 (11.68)	0.566 0.720
<b>Central retinal artery</b>				
RI	0.54 (0.06)	0.50 (0.07)	0.53 (0.05)	<0.001 0.135
PI	0.82 (0.15)	0.72 (0.15)	0.81 (0.15)	<0.001 0.50
EDV (cm/s)	6.02 (1.44)	6.46 (1.01)	5.84 (2.43)	0.262 0.055
PSV (cm/s)	13.50 (3.30)	12.4 (3.0)	12.59 (4.70)	<0.001 0.005
<b>Temporal posterior ciliary artery</b>				
RI	0.53 (0.09)	0.50 (0.09)	0.50 (0.08)	0.021 0.251
PI	0.76 (0.16)	0.70 (0.2)	0.73 (0.17)	0.007 0.156
EDV (cm/s)	6.01 (1.74)	6.01 (1.43)	5.31 (3.36)	0.305 0.372
PSV (cm/s)	13.1 (3.95)	12.20 (4.25)	12.22 (7)	0.365 0.075
<b>Nasal posterior ciliary artery</b>				
RI	0.53 (0.09)	0.50 (0.08)	0.51 (0.07)	0.005 0.029
PI	0.80 (0.23)	0.73 (0.14)	0.73 (0.78)	0.024 0.284
EDV (cm/s)	6.55 (2.35)	6.53 (2.43)	6.91 (2.49)	0.467 0.347
PSV (cm/s)	14.25 (3.68)	13.2 (4.85)	13.9 (5.93)	0.473 0.975

RI; resistance index, PI; pulsatility index, EDV; end diastolic velocity, PSV; peak systolic velocity.

Data are expressed as median (interquartile range).

**3.2. OCTA findings**

In all subjects, baseline and post-vaccination SCP, DCP, FAZ and CCF measurements were obtained using OCTA. There was no statistically significant difference between pre-vaccination and post-vaccination 2nd

**Table 2**  
Optical coherence tomography angiography parameters before and after vaccination.

	Before Vaccine	After 2 weeks	After 4 weeks	P value Pre-after 2 weeks Pre-after 4 weeks
SCP-VD (%)	47 (4.5)	47.1 (4.5)	47.1 (4.0)	NS
DCP-VD (%)	46 (7.2)	46.2 (8.2)	48.0 (6.2)	NS
FAZ (mm <sup>2</sup> )	0.25 (0.16)	0.24(0.18)	0.26 (0.17)	NS
CCF (mm <sup>2</sup> )	2.1 (0.17)	2.1 (0.20)	2.1 (0.18)	NS

SCP-VD; superficial capillary plexus vascular density, DCP-VD; deep capillary plexus vascular density, FAZ; foveal avascular zone, CCF; choriocapillaris flow area, NS; not significantly.

and 4th week values. Pre-vaccine and post-vaccine 2nd and 4th measurements were shown in the [Table 2](#).

**4. Discussion**

Our study findings demonstrated significant changes in retrobulbar ocular circulation using CDUS after CoronaVac compared to pre-vaccination values; however significant change was not observed in terms of retinal microcirculation, detected by OCTA. To the best of our knowledge, this is the first study which investigated the effects of inactivated SARS-CoV-2 vaccine on retrobulbar blood flow with OCTA finding at the same setting.

Adverse event rate was reported between 10–30% after different vaccines. [13] Several types of uveitis, acute macular neuroretinopathy (AMN), multiple evanescent white dot syndrome (MEWS), acute retinal necrosis, acute idiopathic maculopathy, Vogt-Koyanagi-Harada disease and retinal vascular occlusion cases have been reported after hepatitis B, yellow fever, Neisseria meningitis, influenza and herpes zoster vaccines. [14,15] Due to the general use of COVID-19 vaccination in the pandemic, the spectrum of ocular adverse events related to vaccines has also been increasingly reported. [16] Among >10 types of COVID-19 vaccines, numerous ocular adverse effects associated with these vaccines were reported [1]. Several recent studies demonstrated evidence of retinal and choroid-targeted diseases including retinal vein occlusion (RVO), acute macular neuroretinopathy (AMN) and retinal artery occlusion (RAO) in the early phase of SARS-CoV-2 vaccination. [3,17–19] The pathogenesis of SARS-CoV-2 vaccine related side effects has not been clearly elucidated. Commonly proposed mechanisms are reactions caused by adjuvant component of vaccine, molecular mimicry, autoimmunity and hypersensitivity reaction. [20–22]

In inactivated SARS-CoV-2 vaccine, aluminum is thought to cause the immunological side effects, as an adjuvant component. [8] Recently, cases of non-embolic RAO have been reported after COVID-19 vaccination. [17] As non-embolic retinal artery occlusion is known to be associated with hypercoagulation, vasospasm and inflammation [23], an immunological component after vaccination may trigger de novo thrombosis in these cases. In addition, several cases of AMN and paracentral acute middle maculopathy were reported, which were presumed to be caused by subclinical retinal microvascular vasculitis affecting deep capillary layer and choroidal layer after the first dose of inactivated SARS-CoV-2 vaccine. [5,24,25] These abovementioned data regarding to microvascular events and thrombosis after COVID-19 vaccination seem to highlight the importance of screening for retinal vascular involvement in healthy subjects.

In our study, for the first time we evaluated retrobulbar ocular blood flow early after inactive COVID-19 vaccine. Our findings demonstrated significant differences in the retrobulbar blood flow indices in the OA, CRA and PSA at post-vaccination 2nd and 4th weeks. As OA, CRA, PCA are main source of the optic nerve and the retina, the SARS-CoV-2 vaccine may potentially affect the optic nerve, choroidal and retinal vascular supply. Despite the reduction at the post-vaccine 2nd week control, the measured RI, PI of CRA and temporal PCA had a tendency to return initial values at 4th week after vaccination. However significant changes have been detected in the RI, PI, and EDV flow velocities of OA at post-vaccination 2nd week and maintained at the 4th week control. Differences in blood flow characteristics can be found in various ophthalmological diseases, as shown by CDUS. [8] As a result, there is not a clear explanation for the discrepancy regarding retrobulbar blood flow in different arterial measurements. The exact mechanism underlying these effects on the retrobulbar ocular blood flow remains to be determined.

Our study also evaluated the retinal vessel densities and change in microvascular perfusion by means of OCTA in patients after inactive COVID-19 vaccination. We found no significant difference in OCTA measurements after vaccination. Our results were in line with a recent study, which evaluated the OCTA parameters of healthy subjects before

and 1 week after the CoronaVac vaccine [26].

Despite the novelty of our study findings, the change in OCTA and CDUS values were not compatible each other. Although statistically significant difference in retrobulbar blood flow was found, we have not detected any change in OCTA measurements. This might be due to several reasons. Preservation of retinal microcirculation might be due to auto regulatory mechanism in response to vaccine, which may lead to compensation in retinal microvasculature. In addition, retinal circulation is part of the blood retinal barrier whereas the retrobulbar circulation is not. Furthermore, absence of any ocular symptoms and retinal findings in the study participants during the study period might also support the hypothesis of compensation in the microvascular circulation despite the changes in retrobulbar flow. When these findings considered, it should be kept in mind that, our study group comprised of healthy, non-smoking and young subjects without any systemic disease or medication use. When the changes in retrobulbar blood flow in our study group without COVID-19 disease or preexisting systemic diseases considered, potentially more serious retinal vascular complications might be developed in the higher-risk subjects.

In our study, ocular hemodynamics were evaluated at 2nd and 4th week after vaccination. Pichi et al. [24] reported ocular adverse events at a mean time of 5.2 days (range, 1–10 days), whereas Silva et al. [17] evaluated retinal vascular changes at a mean of 10 days (3–16) after COVID-19 vaccination. These data suggest impairment in the ocular blood flow early after vaccination. Therefore, a total of post-vaccination 4-week period seems to be reasonable time period to evaluate the effects of vaccination process. Nevertheless, longer follow-up is needed to elucidate the exact effects of vaccination on ocular hemodynamics.

Our study has some limitations. Firstly, our study is a small scale single-center analysis. Secondly, follow-up period is short, including only 1-months controls after vaccination. Thirdly, we only evaluated the effects of inactivated SARS-CoV-2 vaccine; therefore no data was given regarding the effects of other types of COVID-19 vaccines. As a result, it is unclear if the findings in this specific cohort may be representative of the larger population of worldwide as pandemic evolves. Longitudinal studies investigating microvascular changes over time in this patient group are still needed to elucidate the exact effects vaccination on retinal disorders. Nevertheless, our study is unique in terms of the study population characteristics including healthy subjects without any known COVID-19 infection or vaccination history. As recurrent infections, or previous vaccinations may alter the vascular response, our findings reflect the outcomes in a naive group of subjects after single dose of inactivated SARS-CoV-2 vaccine.

In conclusion, in this study, our findings demonstrated that inactivated SARS-CoV-2 vaccination significantly reduced ocular blood flow, which suggested that vaccination might impair the retinal and choroidal vascular supply. However, inactivated SARS-CoV-2 vaccination did not lead disturbances in microvascular circulation. Further studies are required to better understand the underlying mechanism of adverse effects and determine the exact influence of inactivated SARS-CoV-2 vaccination on retinal hemodynamics.

#### CRediT authorship contribution statement

**Mücella Arıkan Yorgun:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis. **Ozge Sarıtas:** Visualization, Investigation, Data curation. **Erdem Ozkan:** Investigation, Data curation. **Yelda Tascı Yıldız:** Validation, Methodology. **Ozlem Unal:** Methodology, Investigation. **Yasin Toklu:** Supervision.

#### Declaration of Competing Interest

None

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