

## Evaluation of retinal vessel caliber, choroidal thickness, and ocular perfusion pressure in patients with low cardiac ejection fraction

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Received: June 10, 2018 Accepted: December 10, 2018 Published online: April 24, 2019

### ABSTRACT

**Objectives:** This study aims to investigate the retinal vessel caliber, choroidal thickness, and ocular perfusion pressure in patients with low cardiac output.

**Patients and methods:** Between June 2014 and June 2015, a total of 44 patients (34 males, 10 females; mean age 59.3±12.4 years) with low ejection fraction due to dilated cardiomyopathy and 44 healthy, age- and sex-matched individuals (34 males, 10 females; mean age 59.3±8.5 years) were included in this cross-sectional comparative study. All patients in the study group had an ejection fraction less than 40%. Retinal vascular caliber measurements were made using retinal photographs with fluorescein angiography, whereas subfoveal choroidal thickness and foveal thickness were measured using the spectral-domain optical coherence tomography. The ocular perfusion pressure was calculated according to a formula consisting of mean arterial blood pressure and intraocular pressure.

**Results:** There was no statistically significant difference between patients with low cardiac ejection fraction and healthy controls regarding the retinal vascular caliber, subfoveal choroidal thickness, foveal thickness, or ocular perfusion pressure ( $p>0.05$ ). The mean intraocular pressure was 13.1±2.8 mmHg in the study group and 13.4±2.7 mmHg in the control group ( $p=0.59$ ). Ejection fraction was not significantly associated with the retinal vascular caliber, subfoveal choroidal thickness, or ocular perfusion pressure ( $p>0.05$ ).

**Conclusion:** Our findings suggest that reduced cardiac output does not significantly affect the retinal vessel caliber, choroidal thickness, or ocular perfusion pressure in clinical practice.

**Keywords:** Cardiac output, choroidal thickness, foveal thickness, heart failure, ocular perfusion pressure, retinal vessel caliber.

Being associated with progressive hemodynamic deterioration and thromboembolic risk,<sup>[1]</sup> chronic systolic heart failure is often caused by non-ischemic cardiomyopathy (non-ICMP).<sup>[2,3]</sup> Among researches addressing how heart failure affects the eyes,<sup>[4,5]</sup> one reported increased bulbar conjunctival vascular density in mild heart failure, whereas severe heart failure was shown to be characterized by decreased microvascular density.<sup>[4]</sup> Another study reported that chronic heart failure was associated with decreased choroidal thickness.<sup>[5]</sup>

In severe non-ICMP, the heart cannot pump blood well enough to meet the needs of tissue. Following heart failure, tissue hypoxia and peripheral edema, thus, usually develop,<sup>[1]</sup> along with peripheral vascular alterations such as arterial constriction and venous dilation.<sup>[1,4]</sup> By contrast, retinal-choroidal

vessels may not be affected to as great an extent due to strong ocular hemodynamic and vascular protective mechanisms.

In the present study, we aimed to evaluate alterations in retinal-choroidal vascular and foveal thickness in patients with low cardiac ejection fraction (EF). Although ocular blood flow is primarily determined by perfusion pressure and vascular resistance, reduced

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### Citation:

Alur İ, Pekel G, Durna F, Bahar A, Alihanoglu Yİ, Gökşin İ. Evaluation of retinal vessel caliber, choroidal thickness, and ocular perfusion pressure in patients with low cardiac ejection fraction. *Cardiovasc Surg Int* 2019;6(1):1-6.

cardiac output can also affect the ocular vascular structures.<sup>[4,5]</sup> We, therefore, hypothesized that several compensatory alterations may occur in the retinal vessels and choroidal thickness of patients with low cardiac EF due to chronic systolic heart failure.

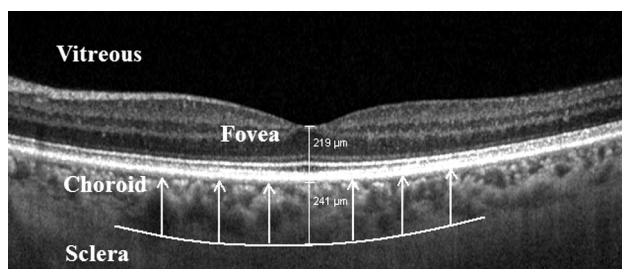
## PATIENTS AND METHODS

This cross-sectional and comparative study was conducted at Medicine Faculty of Pamukkale University, between June 2014 and June 2015. A total of 44 patients (34 males, 10 females; mean age  $59.3 \pm 12.4$  years) with low EF due to dilated cardiomyopathy and 44 healthy, age- and sex-matched individuals (34 males, 10 females; mean age  $59.3 \pm 8.5$  years) were included in the study. All participants were first evaluated by the cardiology and cardiovascular surgery department and later referred to our eye clinic.

A written informed consent was obtained from each patient. The study protocol was approved by the Medicine Faculty of Pamukkale University Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Study population

All patients in the study group were previously diagnosed with dilated cardiomyopathy with an EF  $\leq 40\%$ . Non-ICMP diagnosis was primarily based on echocardiography. No participant exhibited any ocular pathology other than low-grade age-related cataract or was taking ocular medication at the time of the study. Participants with any history of ocular surgery or heart transplantation, with ametropia of greater than two diopters spherical equivalent, or systemic disease such as diabetes mellitus and arterial hypertension which could affect the retinal-choroidal



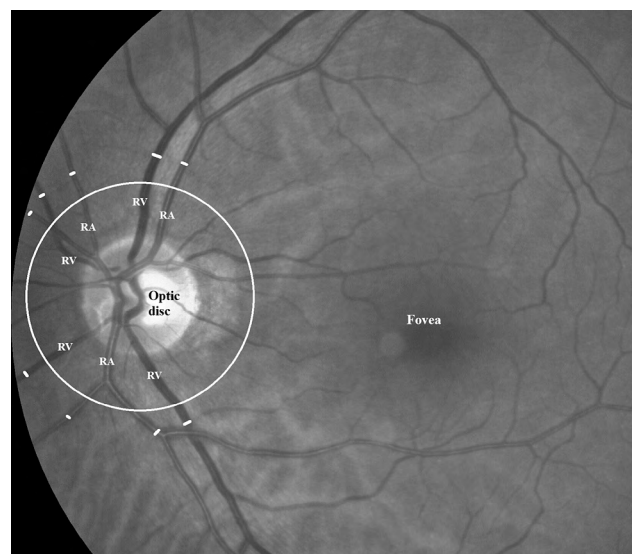
**Figure 1.** Macular enhanced depth optical coherence tomography screen of a patient in whom subfoveal choroidal thickness and foveal thickness measurements were performed.

structures were excluded. Some of the patients in the study group were taking angiotensin-converting enzyme inhibitors or acetylsalicylic acid at the time of the study.

### Ocular examinations

One eye of each participant, chosen at random, was included. All participants received an ophthalmic examination involving the visual acuity assessment, biomicroscopic assessment, air-puff tonometry assessment, retinal examination, ocular perfusion pressure (OPP) calculation, and measurement with spectral-domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg, Germany). The SD-OCT was used to measure the subfoveal choroidal thickness (SFCT) and macular thickness, while the SFCT was measured from the outer part of the hyper-reflective line corresponding to the retinal pigment epithelium to the inner surface of the sclera (Figure 1). The chorio-scleral interface was clearly visualized in all SD-OCT measurements. For macular analysis, only the thinnest foveal thickness was assessed.

Retinal vascular caliber measurements were made using colored retinal photographs with fluorescein angiography (VISUCAM 500, Carl Zeiss Meditec, Jena, Germany). The three largest retinal arterioles and venules passing through an area ranging from one-half to one-disc diameter from the optic disc margin were measured for retinal vascular caliber analysis using manual caliber tools provided by the



**Figure 2.** Retinal vessel caliber analysis method.

RA: Retinal arteriole; RV: Retinal venule.

Table 1 Baseline clinical characteristics of participants			
	Low EF group	Control group	<i>p</i>
	Mean±SD	Mean±SD	
Visual acuity (logMAR)	0.03±0.06	0.03±0.07	0.68
Intraocular pressure (mmHg)	13.1±2.8	13.4±2.7	0.59
Foveal thickness (μm)	222.8±22.3	220.5±15.1	0.57

EF: Ejection fraction.

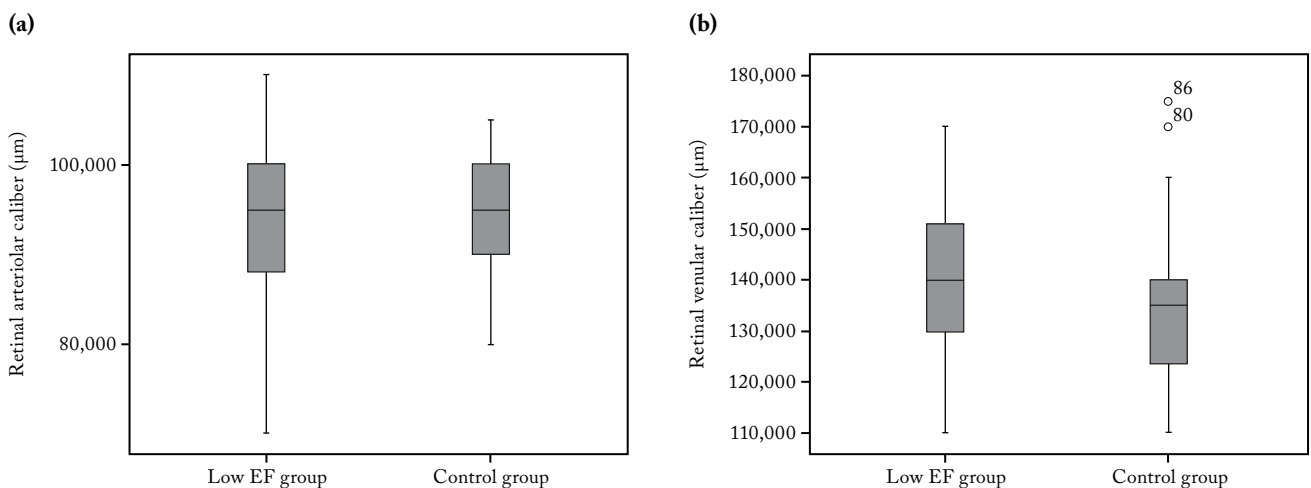
Table 2 Mean retinal vascular caliber and choroidal thickness measurements of participants			
	Low EF group	Control group	<i>p</i>
	Mean±SD	Mean±SD	
Retinal arteriole caliber (μm)	93.0±8.7	93.7±6.8	0.69
Retinal venule caliber (μm)	139.0±15.7	134.4±14.6	0.16
Subfoveal choroidal thickness (μm)	270.6±112.4	280.4±83.6	0.65

EF: Ejection fraction.

fluorescein angiographic device software (Figure 2). The mean caliber values of the retinal vessels were calculated for each participant and recorded for analysis. The intraocular pressure (IOP) was measured with an air-puff tonometer (TonoRef II, Nidek Co. Ltd, Aichi, Japan) and the average of three measurements were recorded. Ocular examinations were performed in the afternoon to eliminate diurnal variation of the measurements. The mean arterial blood pressure was calculated as  $(2/3 \times \text{diastolic blood}$

pressure) +  $(1/3 \times \text{systolic blood pressure})$ , whereas the OPP was calculated as  $(2/3 \times \text{mean arterial blood pressure}) - \text{IOP}$ .<sup>[6]</sup>

All blood pressure measurements were made by a trained nurse using a mercury sphygmomanometer and by monitoring the Korotkoff sounds, preferably on the upper arm. Before being measured for blood pressure, each participant remained seated for at least five minute and was freed of any restrictive clothing on the arms.



**Figure 3. (a)** The box plot graphics for retinal arteriolar caliber and **(b)** retinal venular caliber in low ejection fraction and control groups are shown.

EF: Ejection fraction.

### Statistical analysis

A sample size of 44 for each group was estimated at the beginning of the study by taking the standard effect size 0.60, beta 0.20, and alpha 0.05. Statistical analysis was performed using the PASW version 17.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean±standard deviation (SD). An independent samples t-test was used to compare retinal vascular caliber, SFCT, foveal thickness, and IOP measurements between the study and control groups. The Pearson correlation analysis was used to examine the relationship among retinal vascular caliber, SFCT, OPP, and EF. A *p* value of <0.05 was considered statistically significant.

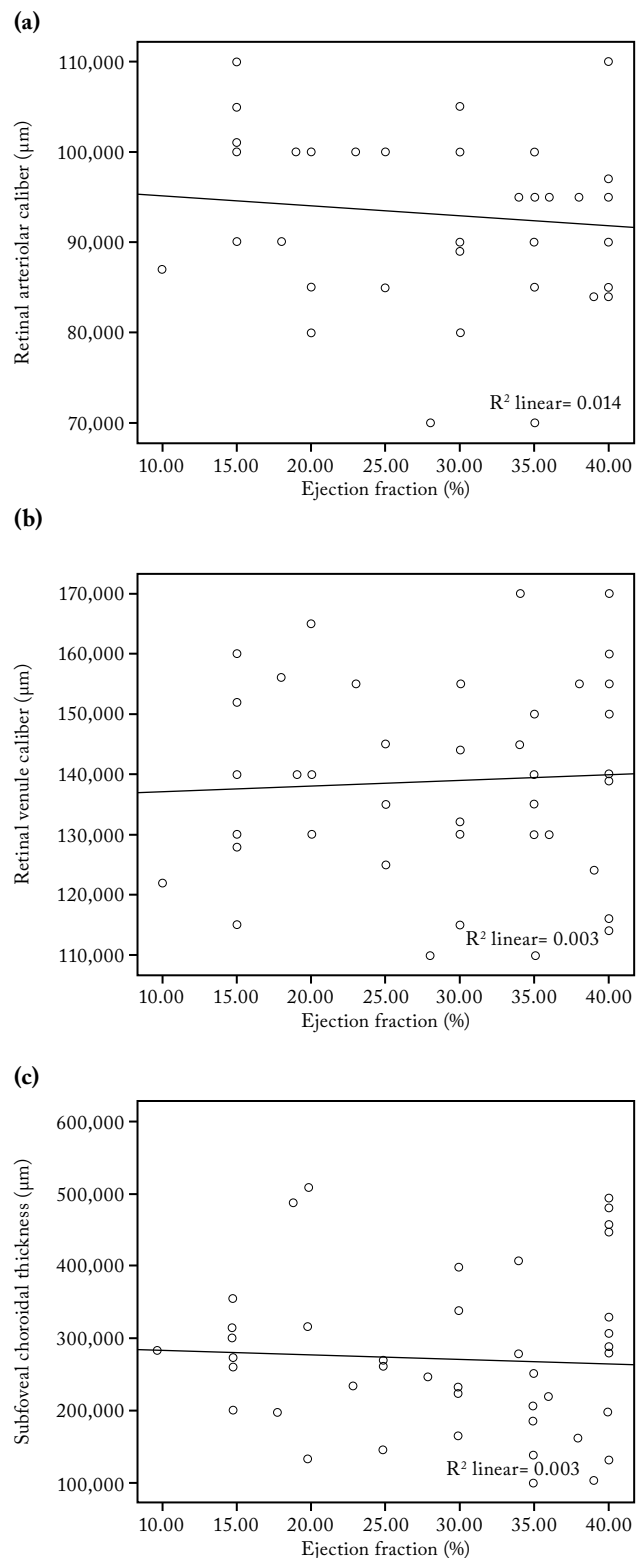
## RESULTS

There were no statistically significant differences between the study and control groups in terms of the baseline characteristics and visual acuity, IOP, or foveal thickness. Table 1 shows clinical characteristics of the study and control groups.

Table 2 shows the retinal arteriole caliber (RAC), retinal venule caliber (RVC), and SFCT measurements of all participants. Although the mean RAC and SFCT values were lower and the RVC values were higher in the study group, there was no statistically significant difference compared to the control group. Figure 3 shows the box plots for RAC (Figure 3a) and RVC (Figure 3b) values in both groups.

Figure 4 is a scatter plot showing the correlation of EF and retinal-choroidal thickness parameters. As Figure 4a shows, as adjusted for age, there was no significant correlation between EF and RAC ( $r = -0.05$ ,  $p = 0.74$ ). As shown in Figure 4b, there was no significant correlation between the EF and RVC ( $r = 0.11$ ,  $p = 0.47$ ). As adjusted for age, EF and SFCT were not correlated ( $r = 0.07$ ,  $p = 0.66$ ) (Figure 4c).

In the study group, the mean systolic blood pressure was  $118.6 \pm 19.9$  mmHg, the mean diastolic blood pressure was  $74.3 \pm 13.8$  mmHg, and the mean OPP was  $46.2 \pm 10.7$  mmHg. There was no statistically significant correlations with OPP and EF ( $r = 0.24$ ,  $p = 0.11$ ), RAC ( $r = -0.12$ ,  $p = 0.45$ ), RVC ( $r = -0.05$ ,  $p = 0.74$ ), and SFCT ( $r = -0.06$ ,  $p = 0.72$ ). Since the RAC, RVC, and SFCT examinations were performed by a single investigator, intra-observer correlation was assessed and the values of RAC ( $r = 0.98$ ,  $p < 0.001$ ), RVC ( $r = 0.98$ ,  $p < 0.001$ ), and SFCT ( $r = 0.99$ ,  $p < 0.001$ ) were found to be high.



**Figure 4.** The scatter plot graphics showing (a) correlations of ejection fraction (cardiac output) with retinal arteriole caliber, (b) retinal venule caliber and (c) subfoveal choroidal thickness.

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## DISCUSSION

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In this study, we investigated the retinal vessel caliber, choroidal thickness, and OPP in patients with low cardiac output. Our results showed that choroidal thickness, retinal vascular caliber, and foveal thickness were similar among patients with chronic systolic heart failure and healthy individuals. Additionally, no significant correlation was observed between EF and retinal-choroidal vessel thickness, and OPP did not significantly affect the RAC, RVC, or SFCT.

Retinal vessel diameter provides information about the microcirculation and can reflect the vascular effects of some systemic diseases.<sup>[7-10]</sup> A narrower RAC is associated with systemic arterial hypertension and coronary heart disease, whereas a wider one is associated with diabetes mellitus, lipid abnormalities, and smoking.<sup>[7-10]</sup> In our study, we found that low cardiac output was associated with neither RVC nor RAC alterations. These outcomes may suggest that the inner retina receives enough blood flow to function properly even with low cardiac output.

Choroidal thickness measurements have become popular, since the development of enhanced depth OCT, and among the various results reported in researches, systemic diseases have been shown to influence choroidal thickness.<sup>[11-14]</sup> The choroidal thickness increases with diabetes mellitus, hypercholesterolemia, and acromegaly, yet decreases with systemic sclerosis.<sup>[11-14]</sup> In our study, however, low EF did not significantly affect the choroidal thickness. In another study, Altinkaynak et al.<sup>[5]</sup> found that SFCT was lower in patients with chronic heart failure, resulting possibly from different patient characteristics or systemic medications used. The aforementioned study included patients who had EF lower than 55%, whereas our study included those with EF lower than 40%.

Several systemic diseases such as diabetes mellitus and arterial hypertension are known to be associated with a thicker macula.<sup>[15,16]</sup> We found that chronic heart failure did not cause any significant increase or decrease in the macular thickness, and the similarity of visual acuity values in the study and control groups might confirm those outcomes regarding the macular thickness. The IOP values were also found to be similar in both groups. In contrast to our results, Meira-Freitas et al.<sup>[17]</sup> reported that chronic heart failure was associated with lower IOP, whereas similar

to our results, Altinkaynak et al.<sup>[5]</sup> found no significant difference in the IOP measurements between the heart failure patients and healthy controls.

Furthermore, several peripheral vascular compensatory mechanisms may contribute to low cardiac EF due to chronic heart failure.<sup>[18]</sup> Choi et al.<sup>[19]</sup> reported that cerebral blood flow decreased with chronic heart failure and their results might be generalized for ocular blood flow, as well. However, the authors found that cerebral blood flow was not associated with EF.<sup>[19]</sup> Although alterations in the RAC, RVC, and SFCT concurred with the peripheral vascular effects of chronic heart failure, the differences were not statistically significant in our study. According to our results, gross pathological ocular vascular alterations in chronic heart failure are unlikely, since patients with such conditions usually do not have visual or ocular problems, as assessed by routine ophthalmological examinations.

Regarding the clinical relevance, our study showed that potential ocular alterations related to low amounts of ocular blood flow in chronic heart failure did not include choroidal thickness or retinal vessel caliber. By contrast, ocular ischemia occurred when a stenosis of 90% of the common or internal carotid arteries was present and retinal-choroidal vascular thickness decreased as a result of low ocular blood flow.<sup>[20,21]</sup> The choroid nourishes the outer retinal layers, and retinal vessels supply blood to the inner retinal layers. The proper functioning of both structures is essential for normal vision, and their anatomy does not change with low cardiac output.

Nonetheless, there are some limitations to this study. First, having fundus fluorescein and indocyanine green angiographies to show additional chorioretinal vascular parameters such as hypoperfusion would have been helpful. Second, the sample size could have been larger, despite the difficulty of identifying low cardiac output patients without any associated systemic diseases. Third, we included patients with heart failure due to low EF in this study. However, EF patients with normal/preserved heart failure are also present. Hence, if an EF with normal/preserved heart failure patient group was available, it might have resulted in a more accurate comparison. Fourth, the EF of the patient group in the study ranged from 30 to 40%. If patients with lower EFs (such as 20 to 30% versus 10 to 20%) were included, interesting results could

have been obtained. Finally, the patients included in the study were those with non-ICPM. If ICMP patients were included, more robust results might have been attained.

In conclusion, low ejection fraction due to chronic systolic heart failure does not significantly alter the retinal vessel or choroidal thickness measurements. Additionally, this condition exerts no significant effect on intraocular pressure, ocular perfusion pressure, or foveal thickness. We, thus, suggest that there is no need to measure cardiac ejection fraction for the evaluation of subfoveal choroidal thickness and retinal vessel caliber. Nevertheless, future studies investigating the effects of coexistent systemic disorders in addition to heart failure would likely clarify the hemodynamic autoregulation of the posterior pole.

#### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

#### Funding

The authors received no financial support for the research and/or authorship of this article.

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