Pak **Heart J**

PERIPAPILLARY RETINAL NERVE FIBER ALTERATIONS IN HEART FAILURE WITH REDUCED EJECTION FRACTION

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Contribution
MNB conceived the idea and designed the study. Data collection and manuscript writing was done by MNB and ME. All the authors contributed equally to the submitted manuscript.

All authors declare no conflict of interest.

This article may be cited as: Bulut MN, Evlice M. Peripapillary Retinal Nerve Fiber Alterations in Heart Failure with Reduced Ejection Fraction. Pak Heart J 2021;54(01):34–39. https://doi.org/10.47144/phj.v54i1.2062

ABSTRACT

Objectives: To evaluate the effect of heart failure with reduced ejection fraction (HFrEF) on retinal nerve fiber layer (RNFL) thickness.

Methodology: The study included patients who were being followed at Kartal Kosuyolu High Speciality Training and Research Hospital for HFrEF and were referred to the Eye Clinic of the Dr. Lütfi Kırdar Kartal Training and Research Hospital, Istanbul, Turkey between 2017-2019. Study participants were divided into two groups, one comprising HFrEF patients and a control group of patients without HF. Each patient underwent a routine ophthalmologic examination including best corrected visual acuity evaluation, intraocular pressure measurement, slit-lamp biomicroscopy and fundus examination. The RNFL of each patient was measured using spectral domain OCT.

Results: A total of eyes of 37 HFrEF patients and 38 controls were evaluated. Superior RNFL thickness was 113.71±17.08 µm in the HFrEF group and 126.22 ± 13.68 µm in the control group (p=0.001). Inferior RNFL thickness was 117.88 ± 14.5 µm in the HFrEF group and 131.69 ± 12.93 µm in the control group (p<0.001). Average RNFL thickness in the HFrEF and control groups was 92.32 ± 10.22 µm and 103.31 ± 8.14 µm, respectively. There were significant differences between the study groups in all five parameters.

Conclusion: In this study, RNLF thinning occurs in HFrEF compared to the control group that may be useful for demonstrate tissue perfusion deficiency in HFrEF.

Keywords: heart failure, ejection fraction, retina

INTRODUCTION

Heart failure (HF) may arise due to structural or functional cardiac defects leading to inadequate cardiac filling or pump function. HF is a complex clinical syndrome characterized by tiredness, shortness of breath with exertion, orthopnea, paroxysmal nocturnal dyspnea, nocturia, alterations of mental state, anorexia and abdominal pain. The terminology used to describe HF is historical and is based on the left ventricle (LV) ejection fraction (EF) measurement. Mathematically, EF is calculated by dividing the stroke volume (i.e. end-diastolic volume minus end-systolic volume) by the end-diastolic volume. Key clinical studies conducted with patients with systolic heart failure (HF), or HF with reduced EF (HFrEF), have generally included patients with EF ≤35%. CHF with ocular perfusion deficiency can also be described as structural or functional cardiac dysfunction resulting in the heart's inability to supply sufficient oxygen to meet the metabolic needs of the tissues, despite normal filling pressures (or with elevated filling pressures).[1]

Obtaining cross-sectional images around the optic disc using optical coherence tomography (OCT) allows the measurement of peripapillary RNFL thickness by quadrant. Substantial RNFL thinning is observed with the onset of glaucomatous optic nerve damage. The ability to quantitatively measure the RNFL prompted studies into the possible utility of RNFL in patients with migraines,[2] Alzheimer's disease,[3] multiple sclerosis,[4] and ischemic cerebrovascular accident.[5] RNFL thinning has also been detected in obstructive sleep apnea syndrome, which can lead to chronic hypoxia and perfusion dysfunction.[6]

With this study we aimed to evaluate the effect of impaired ocular perfusion due to HFrEF on RNFL thickness.

METHODOLOGY

This case-control study included patients who presented at Kartal Kosuyolu High Speciality Training and Research Hospital, Turkey for HFrEF and were referred to the Eye Clinic of the Dr. Lütfi Kırdar Kartal Training and Research Hospital between 2017-2019. The study was in accordance with the rules of the Declaration of Helsinki and the approval of the Dr. Lütfi Kırdar Kartal Training and Research Hospital Local Ethics Committee was obtained. All patients were informed about the study procedure and risks of the treatments, and informed consent forms were obtained.

Study participants were divided into two groups as patients with HFrEF and patients without HF. The HFrEF group included patients with sinus rhythm being followed for chronic systolic HF with LV EF ≤35% as measured by transthoracic echocardiograph (TTE) (biplane Simpson's and Teicholz methods). Patients with carotid stenosis, valvular heart disease or acute HF after myocardial infarction in the previous 6 months, anemia, chronic obstructive pulmonary disease, dyslipidemia and estimated glomerular filtration rate<60mL/min/1.73m^2 were excluded. Volunteers with normal TTE, similar demographic characteristics and no history of any heart disease were enrolled into the control group. Control subjects have not used any systemic medications.

Care was taken to include participants whose general condition allowed compliance with RNFL measurement. Individuals who were not willing to participate in the study, were younger than 18 years old, had previously undergone any ocular surgery, or had a history of systemic steroid use, glaucoma (IOP >21 mmHg, cup-to-disc ratio >0.4, presence of any cup/disc anomalies or visual field defects), other optic neuropathies or neurological disorders, macular pathologies, significant media opacity or high refractive error were excluded. Randomly the left eyes of the HFrEF patients and the left eyes of the control group were evaluated.

HFrEF / control subjects were not under any topical IOP-lowering medication. Patients with diabetes were also excluded from this study. Patients were evaluated for comorbid conditions. Systolic (SP) and diastolic (DP) blood pressure, heart rate (HR), body mass index (BMI), EF and IOP were assessed for patients in both groups. Each patient underwent a routine ophthalmologic examination including best corrected visual acuity evaluation, intraocular pressure measurement by Goldmann applanation tonometer, slit-lamp biomicroscopy and fundus examination. RNFL thickness was measured in all patients using spectral domain OCT (SLO, Optos, Dunfermline, UK). All OCT data were acquired by

the same technician and were evaluated by the same ophthalmologist. SPSS version 22.0 (SPSS for Windows software, SPSS, Inc., Chicago, IL) was used for statistical analyses. The distribution of variables was investigated by Kolmogorov-Smirnov test. Student's t test was used for pairwise comparisons. Statistical significance was set at $p<0.05$.

RESULTS

A total of eyes of 37 HFrEF patients (21 male, 16 female) and 38 controls (23 male, 15 female) were evaluated. Mean SP, DP, HR and BMI was similar in both group.(Table 1)

EF was measured as 26.21±7.79% in the HFrEF group and 61.82±3.34% in the control group. IOP was 17.38±1.91 mmHg in the HFrEF group compared to 17.13±1.88 mmHg in the control group. Thirty patients in the HFrEF group and 28 patients in the control group had a history of smoking. There was a significant difference between the groups in EF ($p<0.001$), while differences in the other variables were not significant (Table 1).

Table 1: Demographic and clinical characteristics of heart failure patients and control subjects

	Control group (n=38)	Heart Failure group (n=37)	*P*
Age, years	57.74 ± 9.05	59.68 ± 10.51	0.39
Gender, n(%) male	23 (60%)	21 (58%)	0.74
Systolic blood pressure, mmHg	127.11 ± 9.06	130.76 ± 9.15	0.11
Diastolic blood pressure, mmHg	78.26 ± 9.03	74.98 ± 6.4	0.11
Heart rate, bpm	71.52 ± 9.97	75.27 ± 8.65	0.15
Body mass index, kg/m^2	24.98 ± 3.97	25.51 ± 3.89	0.77
Smoker, n (%)	28 (73%)	30 (81%)	0.45
Intraocular pressure, mmHg	17.13 ± 1.88	17.38 ± 1.91	0.57
Ejection fraction, %	61.82 ± 3.34	26.21±7.79	<0.001*

According to the New York Heart Association (NYHA) classification, 20 HFrEF patients were class II, 17 were class III.

All HFrEF patients were using diuretic agents, 95.6% were using betablockers, 78.4% ACE inhibitors, 18.9% angiotensin receptor blockers, and 89.2% were using an aldosterone antagonist.

RNFL thickness in the superior, inferior, temporal and nasal quadrant was significantly thinner in HFrEF group. Average RNFL thickness was 92.32±10.22 µm in the HFrEF group and 103.31±8.14 µm in the control group. The differences between the groups were statistically significant in all five RNFL parameters (Table 2). (Figure 1-2)

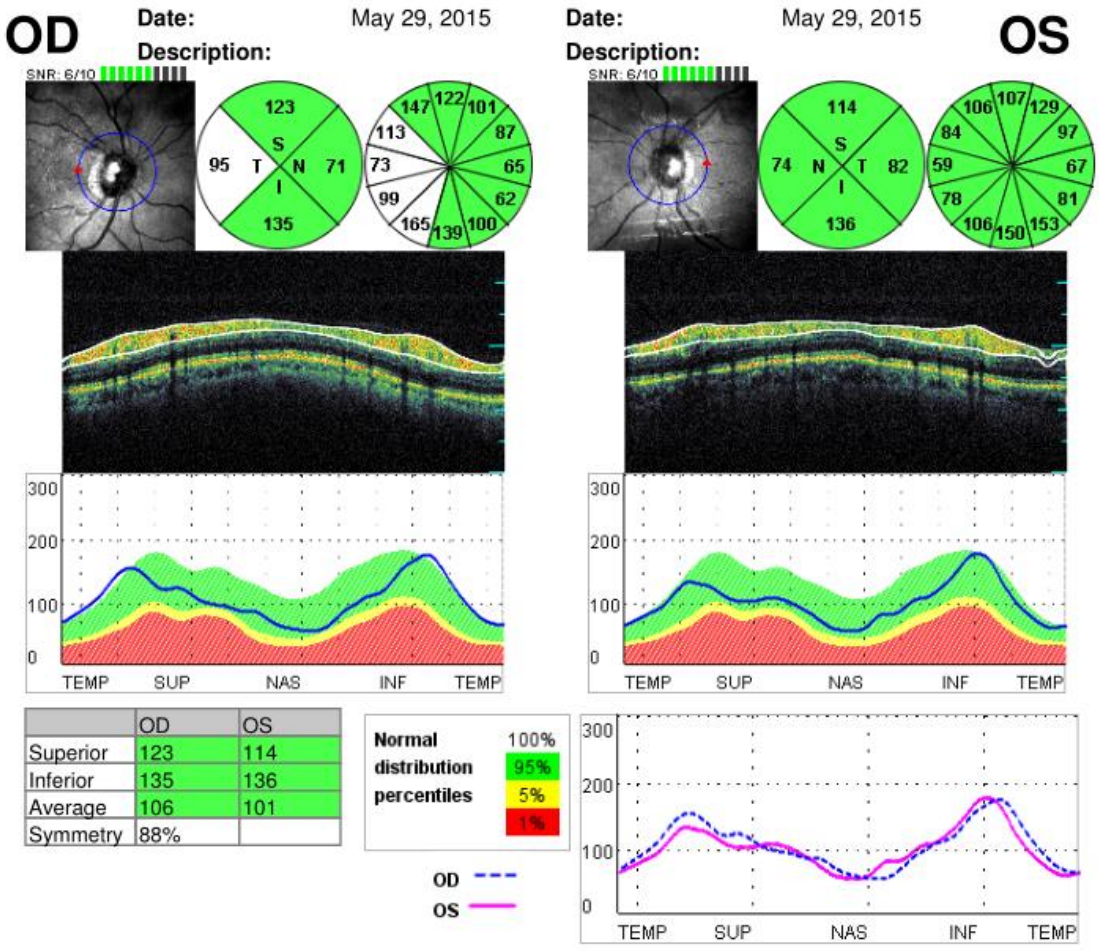
Table 1: Retinal nerve fiber layer thickness in heart failure patients and control subjects

	Control group	Heart failure group	*p value*
OS superior (µm)	126.22 ± 13.68	113.71 ± 17.08	0.001*
OS inferior (µm)	131.69 ± 12.93	117.88 ± 14.5	<0.001*
OS temporal (µm)	77.1 ± 8.42	69.27 ± 9.29	<0.001*
OS nasal (µm)	78.21 ± 8.27	68.41 ± 8.82	<0.001*
OS average (µm)	103.31 ± 8.14	92.32 ± 10.22	<0.001*

*OS: left eye. * Difference is statistically significant (* p<0.01, ** p<0.05)*

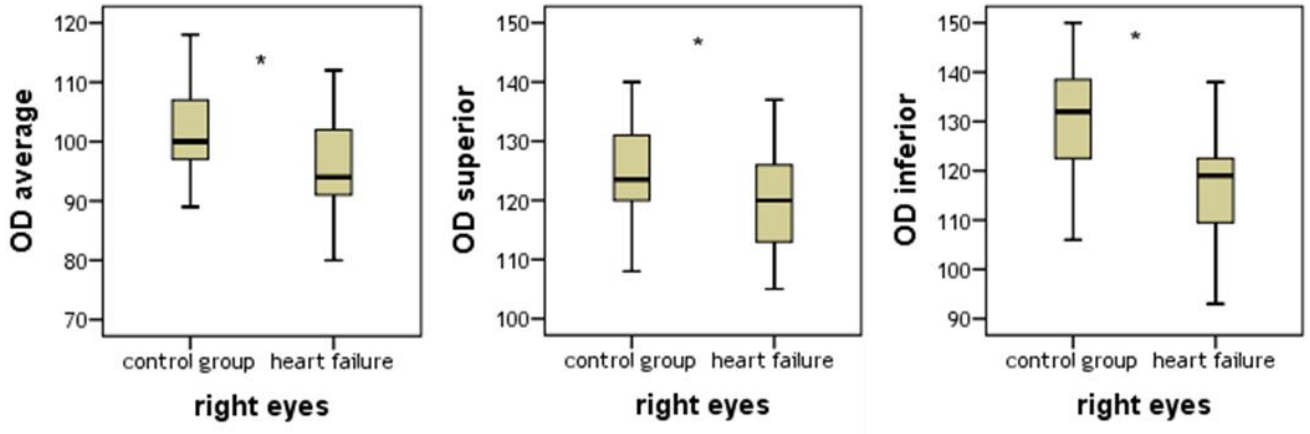
Nineteen patients had ischemic and 18 had non-ischemic cardiomyopathy and left ventricular (LV) ejection fraction (EF) of these two groups were 26.6% and 25.7% ($p <0.62$), respectively, while LV diastolic diameter was 70.1 and 72.8 mm ($p = 0.43$); LV systolic diameter 61.8 and 63.8 mm ($p = 0.60$); interventicular septum 11.4mm and 10.7 mm ($p = 0.43$) and the left atrium diameter that was measured at the parasternal long axis was 45.3 mm and 47.4 mm ($p = 0.07$), respectively. Patients with ischemic cardiomyopathy had significantly more thinning of the RNFL; the mean thickness being 90.9 in this patient group while it was 97.1 in patients with non-ischemic cardiomyopathy ($p = 0.04$).

Figure 1: Measurement of Retinal Nerve Fiber Layer Thickness (RNFL)



INF: inferior, NAS: nasal OD: oculus dextrus, OS: oculus sinister, SUP: superior, TEMP: temporal

Figure 2: Distribution plot of the Retinal Nerve Fiber Layer Thickness (RNFL) in patients with heart failure and controls



** Difference is statistically significant (* p < 0.01, ** p < 0,05). OD: oculus dextrus*

DISCUSSION

In this study we evaluated the relationship between HFrEF and peripapillary RNFL thickness and found that the RNFL is significantly thinner in HFrEF.

Spectral domain OCT (SD-OCT) imaging is utilized to acquire peripapillary RNFL measurements. SD-OCT is used in the early detection and monitoring of glaucoma, and Matlach et al. established the repeatability of measurements taken with different devices.[7] Their comparison of peripapillary RNFL and ganglion cell layer (GCL) thickness measurements from two devices in glaucoma, Parkinson's and ocular hypertension patients versus normal subjects revealed no significant differences. Rao et al. reported that repeated RNFL measurements from the same instrument showed good reliability in both normal eyes and eyes with high myopia.[8] Holló G et al. established that the RNFL exhibited significant differences between glaucomatous and non-glaucomatous eyes.[9] These studies suggest that RNFL measurements may also serve as a sensitive early indicator of CHF-related alterations.

Various studies have been conducted on the association between heart disease and glaucoma. Chen YY et al. stated that primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG) were associated with ischemic heart disease.[10,11] Studies of glaucoma patients reported that rates of ischemic heart disease, migraine and peripheral vascular diseases may be higher in these patients.[12] In their study, Villas-Bôas FDS et al. found a relation between rate of myocardial dysfunction and glaucoma.[13]

In our search of the literature, we found studies regarding ONH pathologies in HF but no detailed investigations of RNFL changes. Meira-Freitas et al. compared 30 HF patients and 30 patients with no cardiac pathology and showed that the HF group exhibited significantly more glaucomatous ONH pathology. However, they found no significant difference between the groups in RNFL reduction.[11] In the current study, the RNFL was significantly thinner in the HF group. A possible explanation for the contradiction between that study and our results is that their HF group included patients with an EF under 55%, whereas we studied patients with EF under 35%.

Gademan, Maaike GJ et al. determined that in HF, blood flow is redistributed via a combination of neural (parasympathetic and sympathetic), humoral (vasopressin, angiotensin, etc.) and local (ions, pH, adenosine, etc.) mechanisms in order to maintain perfusion in vital organs like the brain, heart and intestines.[14] Siesky B et al. claimed that alterations in ocular blood flow may be a cause of glaucomatous damage.[15] Zhu MM et al. stressed that a change in ocular blood flow makes the optic nerve more sensitive to IOP.[16] Consistent with these reports, in our study we found that in HF the optic nerve seems more sensitive to IOP and the RNFL thickness is significant reduced.

A limitation of the current study is that ocular blood flow was not measured by Doppler ultrasonography. Furthermore, medications being used by patients in the CHF group may also cause RNFL thinning as a side effect. For example dehydration due to diuretics may lead to decrease in RNFL thickness. Also due to the asymmetric distribution of functional status of patients, correlation between mean RNFL and functional status was not studied.

The prevalence of HF is increasing in all Western societies, but treating HF and comorbid conditions can greatly improve patients' quality of life. The silent condition normal-tension glaucoma has also been shown to be associated with HF.[17] This demonstrates the importance of RNFL evaluation in HF patients in order to detect subclinical glaucomatous damage and begin treatment with appropriate topical agents.

The results of this study indicate that there is significant thinning of the RNFL in HFrEF. RNFL thinning in HFrEF patients may be useful as an indicator of tissue ischemia due to inadequate perfusion. Also, we concluded that RNFL may be significantly thinned in HFrEF patients provided that there is no concurrent glaucoma or optic neuropathy.

CONCLUSION

As a result, in cases where we cannot understand the reasons that reduced RNFL thickness in eye examination, we need to be careful about conditions such as heart failure that leads to perfusion disorder in all tisues. RNFL thickness measurement may be diagnostic tool for HFrEF. However, in order to comment on the course and treatment of heart failure, large series of studies are needed to be able

to correlate the functional capacity and the RNFL measurement.

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