

Nailfold capillaroscopy findings in cases with rhegmatogenous retinal detachment

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ABSTRACT

Purpose: To compare nailfold videocapillaroscopy (NVC) findings between patients with rhegmatogenous retinal detachment (RRD) and healthy individuals.

Methods: Fifty-five patients that underwent surgery for RRD, who did not have a history of any disease affecting nailfold capillaries and 65 healthy subjects were included in the study. The NVC findings of the RRD group were compared with the healthy control group.

Results: Forty-three (78.19%) of the patients were male and 12 (21.81%) were female in the RRD group. The control group comprised 43 (66.2%) males and 22 (33.8%) females. Among the NVC findings, major (specific) microvascular abnormalities, ectasia, hemorrhage, tortuosity, neoformation, and bizarre and bushy capillaries were statistically significantly higher in the RRD group than in the control group ($p = 0.002$, $p < 0.001$, $p < 0.001$, $p = 0.019$, $p < 0.001$, and $p = 0.05$ respectively).

Conclusion: Nailfold capillaroscopic abnormalities are more frequent in patients with RRD. It has been suggested that there may be a relationship between nailfold microvascular abnormalities and RRD formation at the point of etiopathogenesis.

Keywords: Rhegmatogenous retinal detachment, Nailfold capillaroscopy, Microcirculation

INTRODUCTION

Rhegmatogenous retinal detachment (RRD), the most common type of detachment, occurs by the separation of the neurosensory retina from the retinal pigment epithelium, as a result of fluid accumulation in the subretinal area which originates from the vitreous cavity.¹ To date, risk factors in RRD have been reported as aging, myopia, previous cataract surgery, and ocular trauma. It has been shown that RRD is mostly caused by retinal tears due to vitreoretinal traction; however, this mechanism is not sufficient to explain all cases.²⁻³ Genetic predisposition and inflammation have also been reported to be effective.⁴⁻⁵ In-

flammation and oxidative stress are also known to be important in many vitreoretinal diseases.²⁻⁴

Capillary density, blood flow and capillary abnormalities can be detected with the non-invasive and highly sensitive and specific nailfold videocapillaroscopy (NVC) used to assess the condition of the microvascular bed.⁶ One of the causes of retinal detachments is lattice degeneration, and histological examination of lattice degeneration has shown retinal thinning.⁷ These areas of thinning in the retinal periphery may result from local microvascular changes that can cause ischemia and may be more prone to tear and hole formation. It has been reported that hemorrhage, exudates, and neovascularization seen in diabetic retinopathy result

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from retinal ischemia, which in turn results from retinal capillary abnormalities.⁸ There is no study evaluating nailfold microvascular changes using NVC in patients with RRD. In this study, we aimed to investigate the relationship between systemic microvascular changes using NVC in patients that underwent surgery for RRD in our clinic.

MATERIALS AND METHODS

This case-control study was approved by the local ethics committee of the Antalya Training and Research Hospital with decision number 9/19, and the study was conducted by the ethical standards stated in the Declaration of Helsinki. Before the participants were included in the study, their written informed consent was obtained. No animal subject or plant was included in this study.

The study included patients with RRD who underwent surgery at the Ophthalmology Department of Antalya Training and Research Hospital (RRD group) and healthy subjects (control group). The inclusion criteria for the RRD group were that pseudophakic cases had uncomplicated cataract surgery and that all cases had no systemic disease (hypertension, diabetes mellitus, etc.). Exclusion criteria for both groups were: axial length more than 24 mm, history of eye trauma or concurrent eye disease, smoking or alcohol dependence, history of trauma within the last month, use of antiplatelet, anticoagulant, glucocorticoid, or birth control medications, and being in a high-risk group for microtrauma, such as farmers and gardeners. Patients who had previously undergone eye surgery or had high myopia were not included in the healthy control group.

All patients with RRD and controls evaluated by a comprehensive ophthalmologic examination, best-corrected visual acuity (BCVA) measurement using the Snellen chart, slit lamp anterior and posterior segment examination, and measurement of intraocular pressure (IOP) with Goldmann applanation tonometry.

NAILFOLD VIDEO CAPILLAROSCOPY

The NVC examination was carried out by a single experienced rheumatologist (AA) blinded to the study groups. All NVC examinations were performed at a room temperature of approximately 22-24 °C after resting for at least 20 minutes. In the capillaroscopic evaluation, immersion oil was used for better visualization and the nailfold capillaries of

the second to fifth fingers of both hands were examined with an NVC device (videocap; DS MediGroup, Milan, Italy). Then, 32 images of eight fingers were evaluated according to the criteria of the EULAR working group for morphological and functional parameters, such as capillary density, length, and morphology, visibility of the subpapillary venular plexus, presence of neoangiogenesis or microhemorrhages (at least two pinpoint bleeding foci around a single capillary in at least two fingers), and capillary loop diameter (i.e., dilated capillaries >20 µm, capillary dilation (30–50 µm), and megacapillary vessels >50 µm).⁹ Capillary patterns of healthy controls were defined as red, containing 9–14 U-shaped capillaries (hairpin-shaped loops) per millimeter, parallel to the nail surface.

Capillaroscopic findings are classified as major (specific) and minor (non-specific) abnormalities. Major abnormalities referred to giant capillaries, capillary architecture disorganization like bushy or meandering capillary, microhemorrhages, neoangiogenesis, and avascular areas while minor abnormalities were those with an uncertain pathological meaning, which could be the variation of normal anatomy or a microangiopathy; e.g., tortuosity (with at least two cross capillaries per linear 1 mm), abnormal shapes called bizarre capillaries with abnormal appearance other than previous definitions (cloverleaf, musical note G, etc.), and visibility of the subpapillary venous plexus.¹⁰

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS version 21.0 (SPSS Inc., IL-USA) software. To define the sample, continuous variables were expressed as mean ± standard deviation, and median (minimum-maximum) and categorical variables as number and percentages. The normality of data was tested using the Shapiro-Wilk test in groups with a sample size of <50 the Kolmogorov-Smirnov test in groups with a sample size of >50. In the comparison of the continuous data, the Chi-Square test was applied for the non-normally distributed data and the independent-samples *t*-test for the data with normal distribution. The results were evaluated at the 95% confidence interval, and a *p* value of <0.05 was considered statistically significant.

RESULTS

Fifty-five patients that underwent surgery for RRD between 2017 and 2020 were included in the study. In the

RRD group, 43 (78.19%) patients were male and 12 (21.81%) were female. The control group comprised 65 healthy participants, 43 (66.2%) male and 22 (33.8%) female. The mean age was 59.09 ± 11.55 (range 22-86) years for the RRD group and 59.62 ± 9.45 (range 22-75) for the control group, with no statistically significant difference ($p = 0.792$). Of the patients operated on for RRD, 4 (7.3%) were phakic, 50 (90.9%) were pseudophakic, and 1 (1.8%) patient was aphakic. Four patients underwent combined phacoemulsification and intraocular lens implantation and pars plana vitrectomy (PPV), and one patient underwent PPV with secondary intraocular lens implantation. The mean BCVA value of the RRD group was 0.65 ± 0.60 logMAR and the mean IOP value was 16.34 ± 5.19 , and a statistically significant difference was found compared to the control group ($p < 0.001$ and $p < 0.001$, respectively). The demographic and clinical characteristics of the patients with RRD are summarized in Table 1.

While no aneurysm, avascular area, mega-capillary, meander capillary and extravasation was detected in the RRD

group, ectasia, hemorrhage, tortuosity, neoformation, and bizarre and bushy capillaries were statistically significantly higher in the RRD group than in the control group ($p = 0.002$, $p < 0.001$, $p < 0.001$, $p = 0.019$, $p < 0.001$, and $p = 0.05$, respectively). In the control group, no major capillaroscopic finding was detected except for the non-specific findings of tortuosity and bizarre capillaries. The comparison of the NVC findings between the RRD group and the control group is given in Table 2.

Ten patients (18.1%) had undergone second surgery cause of re-detachment. But there was no statistically significant difference between the group that had re-operated and the group that had been operated once, in terms of NVC findings. Therefore, NVC findings do not seem to be related to the prognosis of surgery.

Examples of specific capillaroscopic findings (ectatic capillary, bizarre capillary, tortuous capillary mega-capillary, and microhemorrhage) demonstrating the presence of microangiopathy are shown in Figure 1.

Table 1: Demographic and clinical characteristics of the patients with RRD

Characteristic	Value	
Age (years)	mean \pm SD	59.09 ± 11.55
	range	(22-86)
Gender	male (n) (%)	43 (78.19%)
	female (n) (%)	12 (21.81%)
Visual acuity (LogMAR)	mean \pm SD	0.65 ± 0.60
IOP (mmHg)	mean \pm SD	16.34 ± 5.19
Glaucoma (n) (%)	10 (18.18%)	
Lens status	phakia (n) (%)	4 (7.3%)
	pseudophakia (n) (%)	50 (90.9 %)
	aphakia (n) (%)	1 (1.8%)
Fundus	reattachment (n) (%)	45 (81.9 %)
	re-detachment (n) (%)	10 (18.1%)
SD, Standard deviation; RRD, Rhegmatogenous retinal detachment		

Table 2. Comparison of the NVC findings between the patients with RRD and the healthy control group			
NVC findings	RRD group (n = 55)	Control group (n = 65)	p value
Capillary ectasia n (%)	6 (11.3)	0 (0)	0.002*
Microhemorrhage n (%)	9 (17)	0 (0)	<0.001*
Tortuosity n (%)	37 (69.8)	8 (12.3)	<0.001*
Neoformation n (%)	4 (7.5)	0 (0)	0.019*
Bizarre capillaries n (%)	23 (43.4)	4 (6.1)	<0.001*
Busy capillaries n (%)	3 (5.7)	0 (0)	0.05*

Bold values represent statistical significance (p < 0.05)

*Pearson Chi-Square test

NVC= Nailfold video capillaroscopy; RRD =Rhegmatogenous retinal detachment

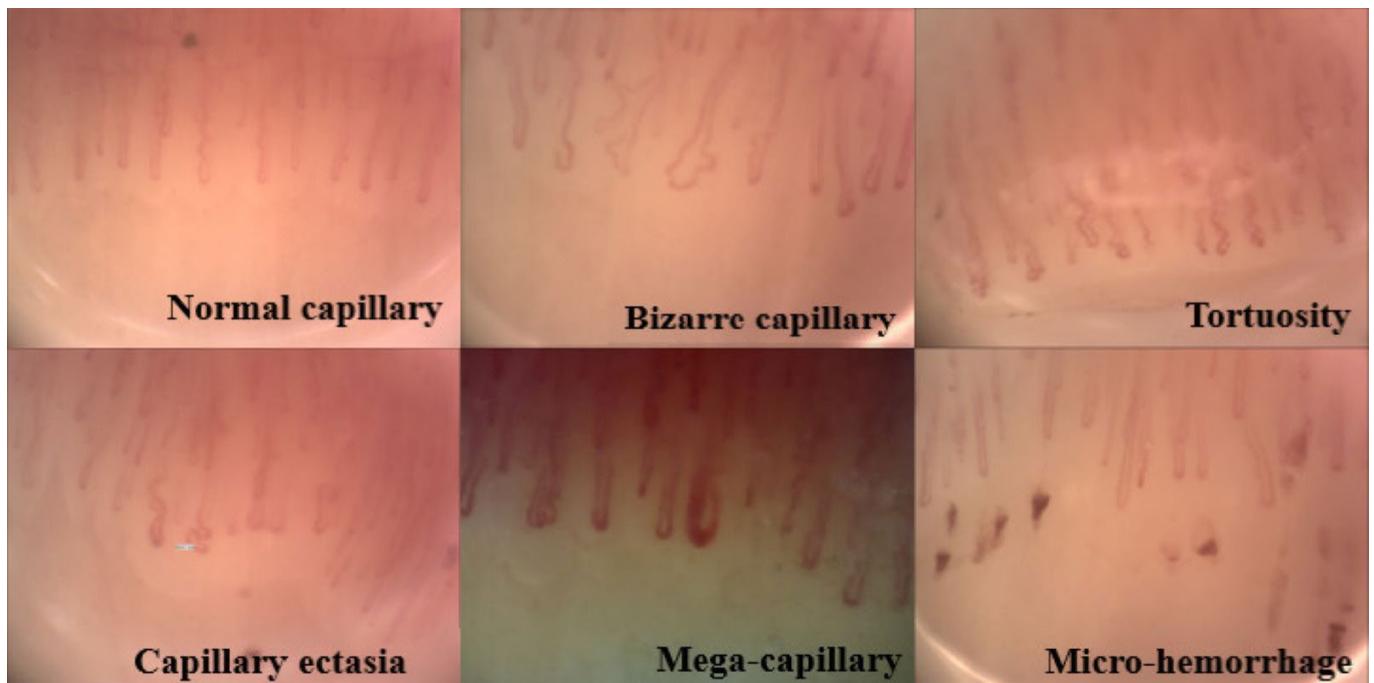


Figure 1. Examples of specific capillaroscopic findings (ectatic capillary, bizarre capillary, tortuous capillary mega-capillary, and microhemorrhage) demonstrating the presence of microangiopathy

DISCUSSION

In current study, we evaluated the NVC findings of patients with RRD and observed major microvascular changes that might be related to oxidative stress and inflammation. It has been reported that RRD is mostly due to local factors of the eye (such as high myopia, high axial length, vitreous aging and degeneration, posterior vitreous detachment, and retinal tears) but it can also be encountered in patients with a normal axial length and no refractive error at advanced age.¹¹ It is also known that some families are susceptible to RRD or a patient with RRD in one eye may develop a tear from the retinal area that appears intact in the fellow eye.⁵ However, the microvasculopathy findings in the current study suggest that local factors as well as systemic factors may be effective in the etiopathogenesis of RRD.

Retinal attachment mainly depends on certain factors, such as the retinal pigment epithelium (RPE) pumping fluid from subretinal space toward the choriocapillaris, the interphotoreceptor matrix glue, healthy (homogeneous) vitreous gel, and in particular the architecture of the vitreoretinal interface.¹²⁻¹⁴ The structure of vitreous body changes by aging and it detaches from the retina.¹⁵ The speed of vitreous changes like degeneration and collapsing depends on environmental oxidative factors and sunlight exposure.¹⁶

Although the vitreous body has many antioxidants protecting the eye from oxidative effects, antioxidant capacity decreases with aging, which is associated with vitreous degeneration.¹⁷ While the eye is constantly affected by oxidative events during all life, light-induced free radicals and metalloproteinase enzyme degradation disrupt the structure of collagen fibrils and adhesion molecules by. The structure of adhesion molecules changes by the years that thought to be an essential factor in formation of retinal tears.¹⁸ As a result of the disruption of collagen fibrils, a tractional force occurs at the vitreous and neurosensory retina interface. This dynamic traction is countered by the cumulative effect of RPE, the interphotoreceptor matrix, and the tensile strength of the retina. The most common complications of posterior vitreous detachment and vitreoretinal traction are retinal tears, vitreous hemorrhage and RRD.¹⁹

Capillaroscopy is a non-invasive, inexpensive, repeatable, diagnostic device designed to evaluate microcirculation intravitally. In 1862, Maurice Raynaud presented local ischemic damage of the hands, feet, nose, and tongue that

became the early vascular signs of several autoimmune diseases and was named 'Raynaud's phenomena'. As first reported by Giovanni Rasori, the relationship between conjunctival inflammation and the changes in nailfold capillaries, many studies have reported the importance of NVC in ophthalmological diseases.²⁰ Tian et al. evaluated the association between nailfold microcirculation and retinal microcirculation in healthy subjects.²¹ They found similarities between both nailfold capillaries and retinal microcirculation. Küçük et al., evaluating the NVC findings of patients with age-related macular degeneration (AMD), reported that the rate of major NVC findings was increased in the AMD group and endothelial dysfunction might play an important role in the AMD pathogenesis, that's thought to be related with ischemia and increased vascular endothelial growth factor (VEGF) level.³ Erol et al. detected dilated capillaries, microaneurysmal dilatation, megacapillaries, microhemorrhage, bizarre capillaries and neoangiogenesis to be more common in the NVC of patients with central serous chorioretinopathy (CSCR).² Oztas et al. reported that CSCR patients have more peripheral retinal degeneration and significantly more lattice degeneration than the control group.²² Chang et al. also reported that CSCR increased the risk of RRD by 7.85 times.²³ As previously reported, CSCR is related to systemic inflammation and oxidative stress. Furthermore, since RRD is often seen in patients with CSCR, it is also considered to be associated with some systemic predispositions.

In this study, we found significant microvascular changes in nailfold microvasculature in patients with RRD. These included ectasia, microhemorrhage, tortuosity, and bizarre and bushy capillaries. Capillary ectasia and microhemorrhages are the earliest signs of capillary damage and may be the indicators of hypoxia and vessel wall damage. Following findings like tortuosity and bushy capillaries are signs of future neovascularization as a result of the increase in production of vascular endothelial growth factor, related to hypoxia.²⁴ Based on NVC findings, the ischemia that may occur contributes to retinal thinning and the easier tear formation in the thinned retina due to traction during posterior vitreous detachment may also contribute to the development of RRD. In our study, the relationship between RRD and the presence of hemorrhage, tortuosity and bizarre capillaries in NVC was found to be more significant than ectasia and neoformation.

As previously reported, choroid capillaries have the same embryological origin as vascular structures such as nailfold capillaries and glomeruli.²⁵⁻²⁶ In addition, histologically, macular, radial peripapillary and nailfold capillaries are all terminal vascular structures with a single layer of endothelium.¹⁸ Giacuzzo et al. measured the choroidal thickness (CT) of eyes with RRD and contralateral eyes and found that cases with peripheral RRD had thinner contralateral CT while the patient with parafoveal or foveal RRD presented with thicker contralateral CT.²⁷ Spencer et al. mentioned that RPE was an interface with choroidal capillary endothelial cells; i.e., systemic circulation.²⁸ A healthy capillary endothelium is important for the differentiation, homeostasis and functions of RPE. In addition, RPE is very important for the neuro-sensorial functioning and attachment of the retina. Capillary endothelial cells also increase the expression of genes related to the extra-cellular matrix. Therefore, any condition that impairs endothelial functions; e.g., hypoxia, inflammation, and oxidative stress will also affect the functions of RPE and the structure of the extra-cellular matrix. We hypothesize that oxidative stress and inflammation play an important role in the etiopathogenesis of RRD. Both sides (the vitreoretinal interface and RPE-capillary endothelial interface) of the neurosensory retina can be affected by these entities locally and/or systematically. As reported in previous studies, adhesion molecules which are a major component of the vitreous body are affected by proinflammatory factors, that would explain the connection between inflammation and RRD.²⁹⁻³⁰

Diederer et al. found increased levels of nitric oxide metabolites in the vitreous body of patients with RRD, which could be activated by endotoxin and cytokines or endothelial activation by glutamate and vasodilators.³⁰ The authors reported that nitric oxide was important for the homeostasis of the eye but its overproduction was neurotoxic and could play a role in the pathogenesis of RRD. Cederlund et al. showed that oxidative stress and antioxidation were important features of RRD.³¹ They measured oxidative stress based on the presence of protein carbonyl groups and antioxidant capacity based on α 1-microglobulin quantity in the vitreous body, and found both to be statistically high in patients with RRD.

Although the literature reports the risk factors causing RRD as high myopia, high axial length, vitreoretinal traction and

retinal tears, autopsy studies have shown that approximately 6 to 11% of individuals over the age of 20 have retinal breaks, but only 0.5% develop RRD.³² Similarly, areas of lattice degeneration have seen in 7 to 8% of adults, but only a small proportion of these lesions progress to retinal detachment.³³ Therefore, linking the etiopathogenesis of RRD only to local factors would be insufficient to explain the etiopathogenesis of the disease. Despite the small number of patients in our study due to the exclusion of those with known systemic diseases and smoking-alcohol use, our study is considered to be valuable since it is the first in the literature on this particular subject. Microvascular abnormalities in our patients support previous research indicating that the presence of inflammation and oxidative stress in the etiopathogenesis of RRD.

Our study also has certain limitations, such as a relatively small sample size and lack of an examination of the biochemical parameters of oxidative stress and inflammation. Our data can be evaluated as preliminary findings to guide future studies with a more comprehensive and prospective design to further investigate biochemical parameters to explain the etiopathogenesis of RRD.

CONCLUSION

In conclusion, the current study involved the comparison of the NVC findings between patients with RRD and a healthy control group. In the RRD group, the rates of ectasia, hemorrhage, tortuosity, neoformation and bizarre capillaries suggesting microvascular circulation disorder in nailfold video capillaroscopy were statistically significantly higher than in the control group. Although we think that microvascular circulation disorders in the peripheral retina may cause rhegmatogenous retinal detachment by causing retinal thinning, holes and tears, more definitive results can be obtained with studies including a larger number of patients.

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