

## Use of nailfold video capillaroscopy in polycythemia vera

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### ABSTRACT

**Objectives:** In this study, we aimed to investigate capillary vessel diameters and structural changes of capillaries by using nailfold video capillaroscopy (NVC) in patients with polycythemia vera (PV).

**Patients and methods:** This cross-sectional study included a total of 24 patients (19 males, 5 females; mean age: 59.8±12.9 years; range, 50.2 to 68 years) who were diagnosed with PV and 15 healthy controls (11 males, 4 females; mean age: 40.7±5.1 years; range, 36 to 44 years) between June 2016 and February 2017. Nailfold video capillaroscopy was performed by an experienced rheumatologist who was blinded to clinical data. The apical, arterial, and venous limb diameters of capillaries were measured and microvascular changes of capillaries were scored.

**Results:** When capillaries were evaluated in terms of morphological structures, giant capillary was detected in 67% of the patients with PV and 0% in the control group ( $p<0.05$ ). The arterial, venous, and apical diameters of the capillaries were significantly higher in the patients with PV compared to the control group ( $p<0.001$ ).

**Conclusion:** The presence of giant capillaries and the marked increase of arterial, venous, and apical diameters of capillaries seem to be related to PV. As it additionally plays an important role in diagnosis, prognosis, and treatment monitoring of certain diseases, capillaroscopy can be considered to be a promising microcirculation biomarker.

**Keywords:** Capillaries, capillaroscopy, nailfold video-capillaroscopy, polycythemia vera.

Polycythemia vera (PV), together with essential thrombocythemia and myelofibrosis, a heterogeneous group of diseases, belongs to the so-called myeloproliferative neoplasms, characterized by the clonal expansion of an abnormal hematopoietic stem/progenitor cell.<sup>1</sup> Thrombotic and hemorrhagic conditions are the most common and serious complications of the

patients with PV. The uncontrolled increase in circulating vascular stasis and erythrocyte mass, as well as endothelial cell damage due to hyperviscosity may cause complications.<sup>2</sup> The incidence of vascular events was high in patients years before the diagnosis of PV was made.<sup>3</sup> An increase in erythrocyte mass, which is one of the causes of hyperviscosity in PV, causes an increase

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in plasma volume, that is one of the causes of complications such as systolic hypertension seen in the course of the disease.<sup>4</sup> As a result of platelet activation over the course of the PV, some occlusive or vasospastic syndromes such as erythromelalgia occur.<sup>5</sup> Erythromelalgia is a condition that occurs as a result of platelet aggregation and platelet-endothelial cell interaction, causing swelling and occlusion of the arterioles temporarily or permanently.<sup>6</sup> It can cause ulceration or necrosis of the affected finger. Erythromelalgia is a syndrome characterized by erythema, warmth and burning, which occurs mainly in the feet, and sometimes in the hands, flaring with hot, position and exercise, and relieves as a result of elevation or cold application of the affected limb.

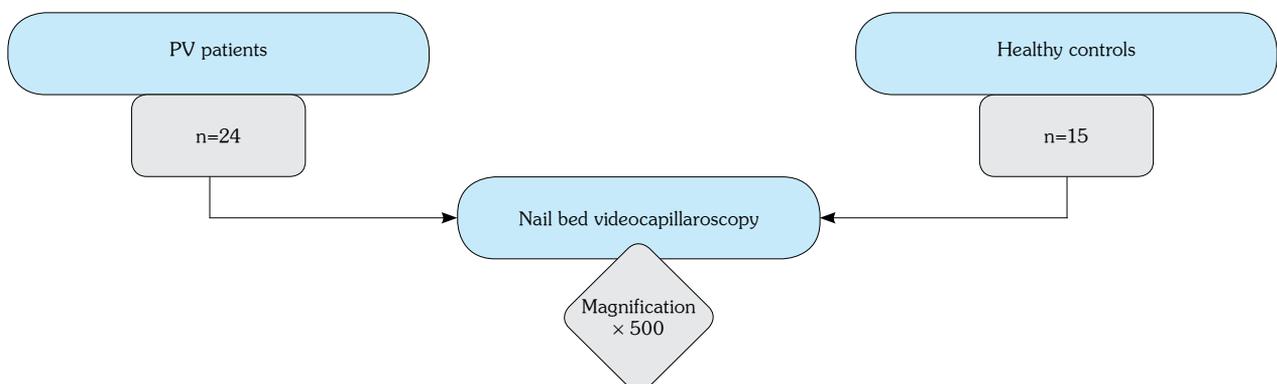
Nailfold video capillaroscopy (NVC) has been used quite frequently in the diagnosis of Raynaud's syndrome and connective tissue diseases in the practice of rheumatology and is a non-invasive, easy, and inexpensive method. It can evaluate morphological changes of capillaries such as folds, elongation, enlargement, crosswise, as well as the measurements of capillary diameters.<sup>7-9</sup> Its results account for diagnostic criteria of systemic sclerosis; however, they can also be useful in staging other connective tissue diseases. The role of NVC as a prognostic tool has been established with the Capillaroscopic Skin Ulcer Risk Index (CSURI), to predict the appearance of new scleroderma ulcers and/or persistence of non-healing lesions, within three months from NVC examination.<sup>10</sup> It has a good sensitivity, specificity, and positive predictive value, even in different devices. Its reliability has been successively demonstrated by the European

League Against Rheumatism (EULAR) study groups.<sup>11</sup>

Capillaroscopy can be useful in the evaluation of prognosis and monitoring the microvascular impact of other systemic diseases. To the best of our knowledge, there is no study using NVC in patients with PV. In this disease group, disorders in peripheral microcirculation may occur. Given this gap in the literature, the primary objective of the current study was to investigate the capillary vessel diameters and structural changes of capillary patients with PV using NVC. The secondary objective was to examine whether there is an appropriate test for the diagnosis of PV patients.

## PATIENTS AND METHODS

This cross-sectional study was conducted at Sakarya Training and Research Hospital, Department of Hematology between June 2016 and February 2017. A total of 24 patients (19 males, 5 females; mean age:  $59.8 \pm 12.9$  years; range, 50.2 to 68 years) who were diagnosed with PV according to the World Health Organization (WHO) diagnostic criteria<sup>1</sup> were included in this study. Demographic data of the patients such as age, sex, body mass index (BMI) and their diagnoses were evaluated by an experienced hematologist, and NVC was performed by a rheumatologist, who was blinded to the patients' data. Nailfold video capillaroscopy was performed in 24 PV patients and 15 healthy controls (11 males, 4 females; mean age:  $40.7 \pm 5.1$  years; range, 36 to 44 years) (Figure 1).



**Figure 1.** Study flow chart.

### Nailfold video-capillaroscopy evaluation

The NVC was performed by an experienced rheumatologist who was blinded to clinical data. The Dino-Lite (AnMo Electronics Corporation, New Taipei City, Taiwan) capillaroscopy device (Dinocapture 2.0 for Windows software; magnification  $\times 500$ ) was used for these evaluations. Additionally, all images were converted to the same calibration as displayed on a 200-magnification lens capillaroscopy device. The NVC device consists of a combination of a digital video camera that can be connected to any computer and an optical microscope. Immersion oil was dropped on the patient's finger cuticle to better visualize the capillaries and reduce refractory defects.<sup>12</sup> After the patient was kept at room temperature for 15 to 20 min, evaluations were made at a temperature of 22 to 23°C, hands at the heart level and the patient in a seated position to prevent changes in the vessel wall.<sup>12</sup> Care was taken not to apply too much pressure on the nail surface, as it interrupts the blood flow and makes it difficult to interpret the images. The evaluations took 15 min for each participant.

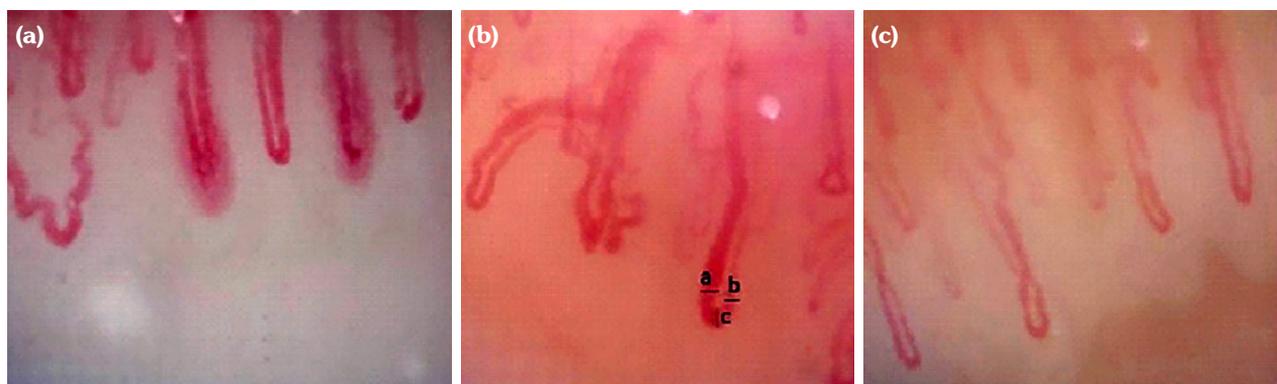
Diameters of capillary, apical, arterial, and venous legs were measured (Figure 2), the presence of giant, ectatic capillary, bleeding areas, avascular areas, and neo-angiogenesis together with the brushy, curved, cross-linked, thin-long capillary shapes were evaluated as described previously in the literature.<sup>12</sup>

### Interpretation of nailfold video-capillaroscopy findings

The NVC was applied to eight fingers (except for the thumbs). A detailed methodology is available in the previous studies.<sup>13,14</sup> Capillaroscopic parameters were recorded for each finger (1 $\times$ 1 mm in size). The diameters of the apical, arterial, and venous legs of the capillary were measured from the fourth finger of the non-dominant hand, since they were less exposed to trauma (Figure 2). Structurally, the frequency of shrub capillary, branched capillary, tortuous capillary, cross capillary, bleeding area, ectasia and giant capillaries were evaluated. After capillaroscopic parameters were evaluated in 1 $\times$ 1 mm area, if more than 50% of capillaries were considered to be affected, it was scored "present". If less than 50% were found to be affected, it was scored as "none". The presence of giant, ectatic capillary and bleeding areas was considered to be "present" even if only one was observed, and if it did not exist, it was evaluated to be "none".<sup>12-14</sup> Capillaries with a diameter greater than  $>50 \mu\text{m}$  were defined as giant capillary.<sup>15</sup> Scoring was done after all images were recorded and numbered anonymously.

### Statistical analysis

The power analysis and sample size calculation were performed using the MedicReS E-PICOS AI Smart Biostatistic SoftWare® version 21.3 (New York, USA). Since there was no



**Figure 2.** Figures (a) and (b) show giant capillary and bleeding areas of PV patients, while Figure (c) shows normal capillaries. Figure (b) shows the measurement of arterial venous and apex diameter.

PV: Polycythemia vera.

capillaroscopy study made with PV patients, a power analysis was performed after 10 patients were included in the study. Power analysis was performed using arterial diameter results. The minimum patient number for each group was found to be 14 with 80% power and 5% (0.05) alpha level.

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean  $\pm$  standard deviation (SD) or median (25<sup>th</sup>-75<sup>th</sup> percentiles), while categorical variables were presented in number and frequency. Comparisons between the two samples were made using the Student t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed variables. The chi-square test was used to compare categorical variables. Analysis of receiver operating characteristics (ROC) curves were performed to determine the cut-off value, sensitivity, and specificity. A *p* value of <0.05 was considered statistically significant.

## RESULTS

This study included 24 patients with PV, the majority of patients with PV, and 15 healthy controls with no disease affecting any peripheral circulation. There was no significant difference between the patient and control groups in terms

of sex and BMI ( $p>0.05$ ). Demographic data of the patients and control group are summarized in Table 1.

The median disease duration of PV patients was 40.50 (range, 9.25 to 99) months, and the median age of CPMD patients was significantly higher compared to the control group (62.50 vs. 40, respectively;  $p<0.001$ ). When the morphological structures of capillaries were examined, no giant capillary was observed in the control group, whereas it was identified in the PV group with a rate of 66.7% ( $p<0.001$ ) (Figure 2). There was no significant difference between the two groups in terms of other morphological parameters. In the PV group, the arterial, venous, and apical diameters of the capillaries were significantly higher than the control group (38.33  $\mu\text{m}$  vs. 21.23  $\mu\text{m}$ , respectively;  $p<0.001$ ), (48.41  $\mu\text{m}$  vs. 27.48  $\mu\text{m}$ , respectively;  $p<0.001$ ), (55.80  $\mu\text{m}$  vs. 36.61  $\mu\text{m}$ , respectively;  $p<0.001$ ) (Table 2).

In the ROC analysis for determining cut-off values for arterial diameter with 83% sensitivity and 80% specificity, 30.10  $\mu\text{m}$  (area under the curve [AUC]: 0.857; 95% confidence interval [CI]: 0.737-0.976;  $p<0.001$ ), for venous diameter with 36.46  $\mu\text{m}$  (AUC: 0.872; 95% CI: 0.762-0.983;  $p<0.001$ ), for apex diameter with 43.85  $\mu\text{m}$  (AUC: 0.852; 95% CI: 0.735-0.969;  $p<0.001$ ) cut-off values (Figure 3).

**Table 1.** Demographic data of PV and the control groups

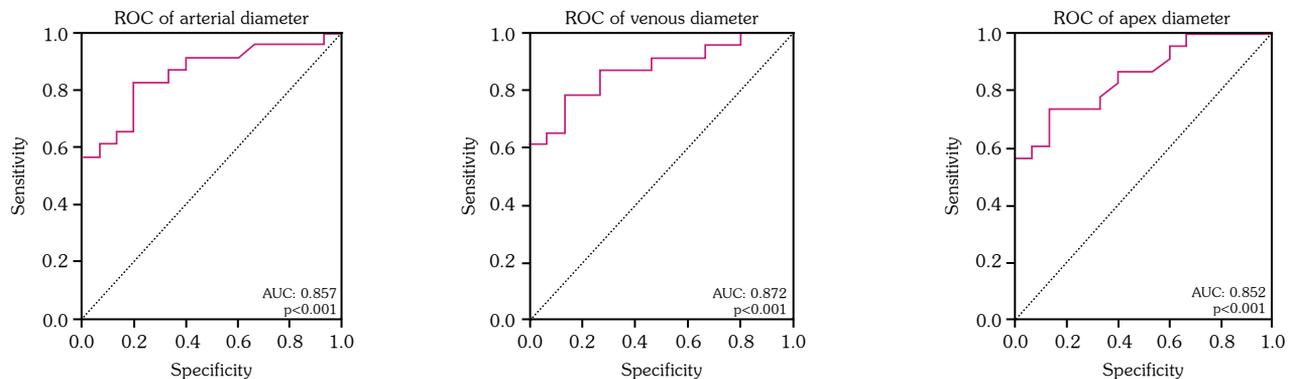
	Control group (n=15)				PV group (n=24)				<i>p</i>
	n	%	Median	25 <sup>th</sup> -75 <sup>th</sup> percentiles	n	%	Median	25 <sup>th</sup> -75 <sup>th</sup> percentiles	
Age (year)			40	36-44			62.50	50.2-68	<b>&lt;0.001</b>
Sex									0.674
Male	11	73.3			19	79.2			
Body mass index (kg/m <sup>2</sup> )			26.34				28.66		0.182
Bush	5	33.3			8	33.3			1
Branched	0	0			2	8.3			0.514
Tortuous	7	46.7			10	41.7			0.759
Cross	14	93.3			22	91.7			0.849
Bleeding area	2	13.3			13	54.2			0.017
Ectasia	8	53.3			10	41.7			0.477
Giant capillary	0	0			16	66.7			<b>&lt;0.001</b>

PV: Polycythemia vera.

**Table 2.** Arterial, venous, and apex diameters of PV and the control groups

	Control group (n=15)		PV group (n=24)		p
	Median	25 <sup>th</sup> -75 <sup>th</sup> percentiles	Median	25 <sup>th</sup> -75 <sup>th</sup> percentiles	
Arterial diameter (µm)	21.23	19.1-29.9	38.33	33.4-47.8	<0.001
Venous diameter (µm)	27.48	24-35	48.41	36.6-54.4	<0.001
Apex diameter (µm)	36.61	27.8-42.1	55.80	39.8-72	<0.001

PV: Polycythemia vera.

**Figure 3.** ROC curve of arterial, venous, and apex diameters.

ROC: Receiver operating characteristics.

## DISCUSSION

Polycythemia vera is a disease that can affect peripheral microcirculation and lead to severe complications caused by hemorrhage and thrombosis. According to our knowledge, there is no study in the literature using NVC in patients with PV. However, with the increase in erythrocyte mass, it can cause significant changes in arterioles. As we expected in this study, we observed that the number of giant capillaries was quite high compared to the control group, indicating the increased erythrocyte mass. It was also observed that the arterial, venous, and apical diameters were significantly higher in the patient group compared to the control group, possibly due to the same reason. However, the limited data on these findings in the literature, no accurate comparison can be made.

Due to the statistically significant difference in the diameter between the two groups, the diameter whether the difference has a value in the diagnosis of PV disease and to determine

which value above would be significant in the diagnosis. The cut-off value was attempted to be found in the current study. In the ROC analysis, the sensitivity was 83% and specificity was 80% in the diagnosis in PV. A diagnostic test is usually considered to have an acceptable diagnostic accuracy, when the sensitivity and specificity is higher than 80%.<sup>16</sup> Therefore, we can speculate that NVC may be a potential diagnostic method for the diagnosis of PV.

The NVC is an easy and practical method for evaluating nailfold microvascular changes, allowing multiple evaluations at once. The presence of giant capillary and remarkable increase in arterial, venous and apex diameters appear to be related to PV. In the present study, the arterial, venous, and apical diameters of the capillaries were significantly higher in the patients with PV group than the control group ( $p < 0.001$ ).

The main limitation of our study is that the sample size is relatively low and no further statistical analysis can be made accordingly. In addition, since 500% magnification in NVC is

not widely used in the rheumatology practice, the absence of a standardized evaluation criterion is among our limitations. A statistically significant difference in age between the PV group and the healthy control group may have also affected the results. Discrete variations, such as tortuous, particularly elderly patients and “meandering” loops and a visible subpapillary venous plexus, may occur, particularly among light-skinned individuals.<sup>17-19</sup> These changes, which can be observed with age, remain within defined normal limits. Therefore, this result may not be an important limitation of our study. Further large-scale, controlled studies are required to identify characteristic capillaroscopic findings specific to PV and to use NVC in the early diagnosis of PV and its complications. Future studies can be planned about the change of these values over time, their importance in early diagnosis, and whether they would allow for follow the parameters.

In conclusion, NVC should be performed to any patient with microcirculation involvement from a systemic disease that includes connective tissue diseases, but also other systemic diseases associated to microangiopathy, such as vasculitis, diabetes, and arterial hypertension. As it additionally plays an important role in diagnosis, prognosis, and treatment monitoring of certain diseases, capillaroscopy can be considered to be a promising microcirculation biomarker.

**Ethics Committee Approval:** The study protocol was approved by the Sakarya Training and Research Hospital Ethics Committee (No: 16214662/050.01.04). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each participant.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions:** Writing the article, literature, revised, control, supervision: E.D.E.; Idea, concept, design: S.B.; Patients collection, prossing: C.S.; Referans and fundings, data collection: Z.E.; Data collection, statistic: S.B.A.; Data collection, plannig, metedology: A.T.

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