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Nailfold videocapillaroscopic changes in patients with pulmonary arterial hypertension associated with connective tissue diseases

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Abstract

Pulmonary arterial hypertension (PAH) represents one of the most devastating complications in connective tissue diseases (CTDs). The aim of this study was to investigate the presence of peripheral microangiopathy in patients with PAH associated with CTDs (CTD-PAH) by exploring nailfold videocapillaroscopic (NVC) changes and identify possible associations of NVC characteristics with markers of disease severity. A cross-sectional study was performed in 18 CTD-PAH patients [13 PAH due to systemic sclerosis (SSc-PAH) and 5 with other types of CTD-PAH], 14 patients with SSc without PAH (SSc-non-PAH) and 20 healthy controls. NVC quantitative and qualitative parameters were evaluated using Optilia Digital Capillaroscope. To ensure inter-observer repeatability, capillaroscopic images were reviewed by two independent investigators. When compared to healthy controls, patients with CTD-PAH (77.8% women, mean age 65.9 years) presented reduced capillary density (6.5 ± 1.6 loops/mm vs. 9.7 ± 0.7 loops/mm, $p < 0.001$) and increased capillary loop width (23.3 ± 10.1 μm vs. 11.2 ± 2.5 μm, $p < 0.001$). SSc-PAH patients presented lower capillary density in comparison with other CTD-PAH patients and SSc-non-PAH subjects and abnormal and disorganized capillaries compared to controls. Patients with other CTD-PAH had also reduced capillary density and increased loop diameter compared to controls. A significant linear correlation was identified between capillary density and estimated glomerular filtration rate in the total CTD-PAH population ($r = 0.63$, $p = 0.007$). In SSc-PAH group, capillary loop diameter was positively correlated to cardiac index ($r = 0.61$, $p = 0.02$). Significant NVC microvascular changes were detected in patients with various types of CTD-PAH, suggesting an impaired peripheral microcirculation parallel to pulmonary vasculopathy.

Keywords Systemic sclerosis · Connective tissue disease · Systemic lupus erythematosus · Peripheral microangiopathy · Nailfold videocapillaroscopy · Pulmonary arterial hypertension

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Introduction

Pulmonary arterial hypertension (PAH) represents a rare and heterogeneous group of pulmonary vasculopathies defined by elevated mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest, normal pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and elevated pulmonary vascular resistance (PVR) ≥ 3 Wood Units [1]. PAH represents one of the most devastating complications in connective tissue disorders (CTD-PAH) with an estimated prevalence of 13% (95% confidence intervals CI 9.1–18.1) [2]. It affects mainly patients with systemic sclerosis (SSc) with an incidence of 18.2 cases per 1000 person-years (95% CI 12.0–27.4) [3], mixed connective tissue disease (MCTD) and systemic lupus erythematosus (SLE), and less frequently patients with dermatomyositis and rheumatoid arthritis (RA) [4]. Beyond common pathogenetic mechanisms with idiopathic PAH such as vasoconstriction, endothelial dysfunction and smooth muscle cells proliferation, a more pronounced inflammatory and autoimmune component has been described in CTD-PAH [5].

Although research in PAH focused primarily on pulmonary vasculopathy, the presence of abnormal biochemical markers of systemic circulation, the correlation between systemic arterial stiffness and microvascular damage, as well as the reduced branchial artery flow-mediated vasodilatation values in patients with PAH are suggestive of a more generalized vasculopathy especially in the SSc spectrum [6–8]. Nailfold videocapillaroscopy (NVC) is a non-invasive method, initially utilized for the differential diagnosis of Raynaud's phenomenon, as it identifies morphological and functional abnormalities in peripheral microcirculation. It is widely used in the diagnosis and follow-up of SSc [9], as different stages of NVC changes may reveal disease progression and convey a prognostic value regarding the risk of developing PAH and internal organ involvement [10–12]. Furthermore, few NVC studies suggested the presence of worse peripheral microvascular dysfunction in patients with PAH associated with SSc or systemic lupus erythematosus (SLE) compared to matched individuals without PAH, as well as in idiopathic PAH compared to healthy controls, supporting the hypothesis that changes in peripheral microcirculation may parallel pulmonary microangiopathy in patients with PAH [13–18].

We aimed to investigate the presence and degree of peripheral microangiopathy in patients with CTD-PAH, explore NVC structural differences among patients with SSc-PAH versus other forms of CTD-PAH and identify possible associations of NVC characteristics with clinical, functional, biochemical and hemodynamic parameters of disease severity in CTD-PAH individuals.

Methods

Study design, setting, and participants

This was a cross-sectional sub-study of a larger observational study conducted at a tertiary center for PH in collaboration with a tertiary center for rheumatic diseases with expertise in NVC in Northern Greece [18, 19]. This study is being reported according to the STROBE guidelines for cross-sectional studies [20]. Adult patients diagnosed with CTD-PAH according to hemodynamic definition of the 2015 European Society of Cardiology Guidelines [21], SSc patients without PAH (SSc-non-PAH) and without significant interstitial lung fibrosis and healthy controls were enrolled between February 2019 and April 2020. All participants fulfilled the revised EULAR/ACR criteria for the diagnosis of SSc [9]. In terms of cardiovascular comorbidities, patients with CTD-PAH and SSc-non-PAH individuals with essential arterial hypertension, atrial fibrillation, diabetes mellitus and severe left ventricular dysfunction were excluded from this study. Written informed consent was obtained from all participants. The study received approval from the Aristotle University of Thessaloniki Ethics Committee and performed according to the Declaration of Helsinki.

Patients with CTD-PAH were either newly diagnosed and treatment naïve, as far as PAH-specific therapy was concerned, or had established PAH and were receiving targeted treatment. CTD-PAH individuals underwent physical examination, electrocardiography, 6-min walking test (6MWT), right heart catheterization (RHC), spirometry with measurement of CO diffusing capacity (DLCO%), high-resolution computed tomography (HRCT) to exclude significant lung fibrosis and NVC within the same 1-week time interval. Cardiac index was measured with the method of thermodilution. SSc-non-PAH subjects underwent physical examination, spirometry with measurement of CO diffusing capacity and NVC within the same time interval. Pulmonary hypertension (PH) was excluded in SSc controls by transthoracic echocardiography (TTE) or RHC; the latter conducted in case TTE findings were suspicious for the presence of PH. Significant interstitial lung fibrosis was excluded with HRCT. Both CTD-PAH and SSc-non-PAH individuals underwent laboratory evaluation with blood samples collected at the same time interval, including hemoglobin, uric acid, creatinine, and autoantibodies (anticentromere autoantibodies, antinuclear autoantibodies and anti-topoisomerase autoantibodies). In CTD-PAH individuals, N-terminal pro-brain natriuretic peptide was also evaluated. Estimated glomerular filtration rate (eGFR) was calculated based on the 4-variable Modification of Diet and Renal Disease (MDRD) equation. Healthy controls underwent clinical examination and NVC.

Nailfold videocapillaroscopy technique and image analysis

NVC was performed at room temperature (22–23 °C) with the subject seated and resting for 15 min. Optilia Digital Capillaroscope (Optilia Instruments AB, Sollentuna, Sweden) was used for image acquisition (200 × magnification). One drop of immersion oil was applied on the nailfold to maximize the transparency of the keratin layer. At least two adjacent fields of 1 mm in the middle of the nailfold were captured from all hands excluding thumbs. In total, 16 images from each patient were captured, coded, saved and manually analyzed using Optipix Lite software (Optilia Instruments AB). To ensure inter-observer repeatability, the stored pictures were reviewed by two independent investigators (EP and ET) blinded to the clinical data.

NVC images were quantitatively and qualitatively assessed. The following quantitative parameters were measured: capillary density (number of capillary loops per linear mm measured in the distal row following the 90° method) [22], avascular areas [23] (distinct areas in the nailfold where two or more capillaries are missing), capillary dimensions [23] (total capillary width and capillary loop width; the mean value of each dimension of all capillaries per linear mm was eventually calculated), hemorrhages (defined as the presence of at least one hemorrhage in at least two different NVC images) and number of hemorrhages per linear mm, thrombosis (number of thrombi per linear mm), edema (defined as the presence of edema in ≥ 50% of assessed fingers) and capillary morphology (abnormal capillary shapes and architectural disorganization per linear mm).

As irregularly enlarged were characterized capillaries with loop width > 20 µm and < 50 µm and as giant, homogeneously enlarged capillaries with loop width ≥ 50 µm [24]. The mean of each capillaroscopic feature was calculated from the sum of consecutive images for each digit. Subsequently, the average values from the eight fingers were added together and divided by the number of studied digits. The resulting value indicated the number of a certain capillaroscopic feature adjusted by each millimeter of the nailfold.

The "overall pattern recognition" was qualitatively assessed based on capillary density, the presence of irregularly enlarged or giant capillaries, hemorrhages and shape abnormalities using a fast-track algorithm proposed by Smith et al. [25, 26]. Images were classified as "normal pattern", "non-specific pattern" and "scleroderma pattern". Furthermore, a semi-quantitative rating scale was adopted (score 0–3) to classify patients according to the severity of systemic microvascular disease. Capillary density was rated as follows: 0 for > 9 capillaries/mm, 1 for 7–9 capillaries/mm, 2 for 4–6 capillaries/mm and 3 for 1–3 capillaries per mm [27, 28]. Irregularly enlarged capillaries, giant capillaries, hemorrhages and shape abnormalities were scored accordingly: 0 equals to no changes, 1 to changes less than 33% of the total number of capillaries/mm, 2 to changes between 33 and 66% of the total number of capillaries/mm, and 3 to changes more than 66% of the total number of capillaries/mm [27, 28]. The total score was calculated by the sum of scores for each finger divided by the total number of fingers evaluated and was rounded to the next integer to define the risk group.

Statistical methods

Data are presented as mean ± standard deviation or as median (interquartile range, IQR) for continuous variables. Normal distribution was assessed using the Shapiro–Wilk test. Differences between two independent categories with respect to quantitative variables were analyzed using the Student's *t* test for independent variables or the Mann–Whitney test. Differences among more independent groups were tested with one-way ANOVA or the Kruskal–Wallis test, and post hoc analysis with adjustment for multiple comparisons (Bonferroni test).

Categorical variables are presented as absolute count and percentage (%) and were analyzed using the Chi-square test or Fisher's exact test when appropriate. The reproducibility of the semi-quantitative rating scale was evaluated using Cohen's kappa coefficient.

Pearson or Spearman coefficient (*r*) was used to explore the correlation between capillaroscopic parameters and functional, laboratory and hemodynamic parameters. Univariable and multivariable linear regression analyses were performed to control for potential confounders such as age and DLCO% (Supplementary File). For normally distributed variables, linear equation with 95% confidence intervals (CI) is also presented. A p value < 0.05 was considered statistically significant. Data were analyzed using IBM SPSS statistics (version 26.0) software.

Results

Baseline characteristics

In total, 18 consecutive patients with CTD-PAH (77.8% women, mean age 65.9 ± 10.2 years), 14 patients with SSc-non-PAH (92.8% women, mean age 55.6 ± 13.4 years) and 20 healthy controls (75% women, mean age 56.3 ± 8.6 years) were included in the study. Demographic data and disease characteristics are summarized in Table 1. CTD-PAH group consisted of 13 patients with PAH associated with SSc (SSc-PAH), of whom 10 patients with diffuse SSc and 5 patients with PAH associated with other CTD (2 patients with SLE and 1 patient with RA, MCTD and spondyloarthritis, respectively). Half of CTD-PAH patients were newly diagnosed

Table 1 Baseline demographics and disease characteristics

Variables	Total CTD-PAH	SSc-PAH	Other CTD-PAH	SSc-non-PAH	Healthy controls	P_1 value*	P_2 value**
N	18	13	5	14	20		
Incident, *n* (%)	9 (50.0)	6 (46.2)	3 (60.0)	0			
Disease duration (months)	70 (150)	80 (174)	60 (143)	60 (77)	–	0.32	0.20
Duration from PAH diagnosis (months)	4 (38)	6 (39)	2 (29)	–	–	–	0.96
Female, *n* (%)	14 (77.8)	10 (76.9)	4 (80.0)	13 (92.8)	15 (75.0)	0.39	0.60
Age, years	65.9 ± 10.2[+#]	68.4 ± 8.1[§$]	59.6 ± 13.5	55.6 ± 13.4[$#]	56.3 ± 8.6[§+]	0.009	0.008
BMI, kg/m^2	27.2 ± 4.6	27.4 ± 4.4	26.8 ± 5.6	26.8 ± 5.8	24.7 ± 3.1	0.26	0.44
Diffuse SSc		10 (76.9)	–	7 (53.8)	–		0.4
Raynaud's, *n* (%)	15 (83.3)	12 (92.3)	3 (60.0)	12 (85.7)	–	0.46	0.16
Duration of Raynaud's, (y)	16.3 ± 12.9	15.6 ± 14.1	16.1 ± 13.2	10.0 ± 9.2		0.14	0.14
Telangiectasias	7 (38.8)	7 (53.8)	0	2 (14.3)		0.22	0.02
Digital ulcers	2 (11.1)	2 (15.4)	0	1 (7.7)		1.0	0.54
WHO FC							
II/III	10 (55.6)/8 (44.4)	7 (53.8)/6 (46.2)	3 (60.0)/2 (40.0)				0.1
6-MWD (m)	405.7 ± 126.7	369.3 ± 113.9	539.3 ± 73.2				0.03
Laboratory tests							
Hb (g/dl)	12.7 ± 1.3	12.6 ± 1.2	13.1 ± 1.7	13.1 ± 1.1		0.41	0.56
eGFR, ml/min/1.73m^2	75.6 ± 27.1	68.1 ± 21.7	93.8 ± 32.7	80.9 ± 21.9		0.56	0.12
Uric acid, mg/dl	5.5 ± 1.4	5.4 ± 1.2	6.2 ± 2.5	4.2 ± 1.6		0.04	0.09
NT-proBNP (pg/ml)	933 (2508)	1016 (2418)	851 (8829)			–	0.73
ANA (≥ 1/160)	10 (50.0)	6 (46.1)	4 (80.0)	9 (64.3)		0.61	0.37
ACA	3 (16.7)	2 (15.4)	1 (25.0)	4 (28.6)		0.17	0.22
Anti-Scl-70	2 (11.1)	2 (15.4)	0	1 (7.7)		1.0	1.0
Right heart catheterization (RHC)							
mRAP, mmHg	5.9 ± 3.4	5.5 ± 3.1	7.0 ± 4.3				0.44
mPAP, mmHg	40.2 ± 9.1	39.7 ± 7.1	41.4 ± 10.2				0.74
CI, ml/m^2	3.1 ± 1.2	2.7 ± 0.7	3.9 ± 1.9				0.07
PVR, WU	6.6 ± 4.0	6.9 ± 4.3	5.8 ± 3.5				0.64
LFTs							
FEV1/FVC%	77.4 ± 12.1	78.5 ± 13.4	74.7 ± 9.2	82.6 ± 5.2		0.24	0.42
DLCO%	56.6 ± 22.7	53.6 ± 23.2[$]	65.8 ± 22.7	83.6 ± 15.1[$]		0.002	0.007
PAH treatment, *n* (%)	10 (61.1)	8 (61.5)	2 (40.0)				
Monotherapy	5 (27.8)	5 (38.4)	0	1 (7.7) [++]			
Dual therapy	3 (16.7)	1 (15.4)	2 (40.0)	0			
Triple therapy	2 (11.1)	2 (7.7)	0	0			

Categorical variables are presented as frequency and percentage, *n* (%). Continuous variables are presented as mean value ± standard deviation or median value with interquartile range

ACA anticentromere autoantibodies, *ANA* antinuclear autoantibodies, *anti-Scl-70* anti-topoisomerase autoantibodies, *BMI* body mass index, *6-MWD* 6-min walk distance, *bpm* beats per minute, *CI* cardiac index, *CTD-PAH* pulmonary arterial hypertension associated with connective tissue disease, *DLCO* diffusing capacity for carbon monoxide, *FC* functional class, *FEV1* forced expiratory volume during the first second of expiration, *FVC* forced vital capacity, *GFR* glomerular filtration rate, *mPAP* mean pulmonary artery pressure, *mRAP* mean atrial pressure, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *PAH* pulmonary arterial hypertension, *PVR* pulmonary vascular resistance, *SSc* systemic sclerosis, *SSc-PAH* pulmonary arterial hypertension associated with systemic sclerosis, *SSc-non-PAH* systemic sclerosis not complicated with PAH, *WHO* World Health Organization, *WU* wood unit

*P_1 value refers to differences among total CTD-PAH cohort, SSc-non-PAH patients and healthy controls. **P_2 value refers to differences among SSc-PAH, other CTD-PAH, SSc-non-PAH and healthy controls. For variables in which there is no value in certain columns, then p_1 and p_2 refer to differences among the remaining groups. Statistical significance is defined as $p < 0.05$

Post hoc analysis was performed to find statistical significance among subgroups as follows:

[+]Statistical significance between total CTD-PAH and SSc-non-PAH. $p < 0.05$

[#]Statistical significance between total CTD-PAH and controls. p value < 0.05

[$]Statistical significance between SSc-PAH and SSc-non-PAH. p value < 0.05

[§]Statistical significance between SSc-PAH and controls. p value < 0.05

[++]Patients with SSc received endothelin receptor agonists due to digital ulcers

and received no specific PAH treatment at the time of NVC examination, while 27.8% of prevalent patients were on monotherapy. Median duration from diagnosis for prevalent PAH patients was 4 (38) months, while the duration of diagnosis for the underlying CTD did not differ significantly between CTD-PAH and SSc-non-PAH patients. One patient with SSc-non-PAH received endothelin receptor antagonists for digital ulcers and 38.4% were on a calcium channel blocker either as an antihypertensive or as Raynaud's treatment. CTD-PAH patients had worse DLCO% than SSc-non-PAH group (56.6 ± 22.7% vs. 83.6 ± 15.1%, $p = 0.002$).

Capillaroscopic alterations in CTD-PAH

The majority of quantitative and qualitative capillaroscopic parameters were abnormal in patients with CTD-PAH as compared to healthy controls (Table 2). Capillary density was significantly reduced in the total CTD-PAH population (6.5 ± 1.6 loops/mm), but also in the SSc-PAH (6.1 ± 1.4 loops/mm) and the other CTD-PAH group (7.8 ± 1.3 loops/mm) compared to healthy controls (9.7 ± 0.7), ($p < 0.001$) (Fig. 1). In addition, SSc-PAH presented lower capillary density in comparison with other CTD-PAH patients and SSc-non-PAH subjects (Fig. 1). SSc-PAH patients had also more avascular areas on capillary nailfold compared to other CTD-PAH patients.

In terms of capillary dimensions, total capillary width was much higher in total CTD-PAH cohort compared to SSc-non-PAH ones, a difference mainly attributed to SSc-PAH group. Furthermore, loop diameter was increased in all groups of patients compared to controls. Irregularly enlarged and giant capillaries were present at the same extent in the CTD-PAH cohort and SSc-non-PAH subjects compared to healthy controls. Capillary edema, microhemorrhages and capillary thrombi were detected both in SSc-PAH and in other-CTD-PAH patients at a significant extent. Finally,

Table 2 Capillaroscopic alterations among patients with CTD-PAH, SSc-non-PAH subjects and healthy controls

	Total CTD-PAH	SSc-PAH	Other CTD-PAH	SSc non-PAH	Healthy controls	P_1 value*	P_2 value*
N	18	13	5	14	20		
Avascular areas (n/mm)	$1.0 \pm 0.6^{\#}$	$1.2 \pm 0.2^{£§}$	$0.6 \pm 0.6^{£}$	$0.9 \pm 0.4^{¥}$	$0.15 \pm 0.2^{\#¥§}$	< 0.001	< 0.001
Avascular areas, *N* (%)	16 (88.8)	13 (100.0)	3 (60)	12 (85.7)	6 (30.0)	< 0.001	< 0.001
Total capillary width (μm)	$58.5 \pm 24.8^{\#+}$	$62.4 \pm 28.2^{\$\$}$	48.4 ± 7.6	$42.8 \pm 9.5^{+\$}$	$29.2 \pm 4.2^{\#\$}$	< 0.001	< 0.001
Loop width (μm)	$23.3 \pm 10.1^{\#}$	$24.5 \pm 11.7^{\$}$	$20.1 \pm 1.6^{\dagger}$	$18.6 \pm 4.9^{¥}$	$11.2 \pm 2.5^{\#¥\S\dagger}$	< 0.001	< 0.001
Irregularly enlarged capillaries (loops/mm)	$1.9 \pm 0.6^{\#}$	$1.7 \pm 0.5^{\$}$	$2.3 \pm 0.9^{\dagger}$	$2.1 \pm 1.2^{¥}$	$0.3 \pm 0.4^{\#¥\dagger\$}$	< 0.001	< 0.001
Giant, *N* (%)	7 (38.8)	6 (46.1)	1 (20.0)	3 (21.4)	–	0.44	0.32
Edema, *N* (%)	9 (50)	7 (53.8)	2 (40)	7 (50.0)	–	1.0	0.87
Microhemorrhages (*n*/mm)	0.25 (0.4)	0.2 (0.5)	0.3 (0.3)	0.24 (0.3)	–	0.59	0.82
Microhemorrhages, *N* (%)	10 (55.5)	7 (53.8)	3 (60)	7 (50.0)	–	1.0	0.97
Thrombosis (*n*/mm)	$2.5 \pm 1.2^{\#}$	$2.6 \pm 1.0^{\$}$	2.2 ± 1.8	$2.6 \pm 0.9^{¥}$	$1.5 \pm 0.7^{\#¥\$}$	0.002	0.004
Disorganized capillaries (loops/mm)	$1.0 \pm 0.7^{\#}$	$1.0 \pm 0.7^{\$}$	0.9 ± 0.7	0.8 ± 0.5	$0.2 \pm 0.4^{\#\$}$	0.001	0.003
Shape abnormalities (loops/mm)	$2.2 \pm 1.0^{\#}$	$2.3 \pm 1.0^{\$}$	1.7 ± 1.2	1.8 ± 0.8	$1.2 \pm 0.8^{\#\$}$	0.009	0.01
Ramified capillaries (loops/mm)	$0.8 \pm 0.7^{\#}$	$0.9 \pm 0.7^{\$}$	0.5 ± 0.4	0.4 ± 0.3	$0.2 \pm 0.2^{\#\$}$	0.004	0.005

Categorical variables are presented as frequency and percentage, *n* (%)

Continuous variables are presented as mean value ± standard deviation or median value and interquartile range

CTD-PAH pulmonary arterial hypertension associated with connective tissue disease, *SSc* systemic sclerosis, *SSc-PAH* pulmonary arterial hypertension associated with systemic sclerosis, *SSc-non-PAH* systemic sclerosis not complicated with PAH

*A p value < 0.05 is considered statistically significant. P_1 value demonstrates differences among CTD-PAH, SSc-non-PAH and controls. P_2 value demonstrates differences among SSc-PAH, other CTS-PAH, SSc-non-PAH and controls. For columns that there is no value in control group, significant differences account for the remaining groups

Post hoc analysis was performed to find statistical significance among subgroups as follows:

[+]Statistical significance between total CTD-PAH and SSc-non-PAH. $p < 0.05$

[#]Statistical significance between total CTD-PAH and controls. p value < 0.05

[¥]Statistical significance between SSc-non-PAH and controls. p value < 0.05

[$]Statistical significance between SSc-PAH and SSc-non-PAH. p value < 0.05

[£]Statistical significance between SSc-PAH and other CTD-PAH. p value < 0.05

[§]Statistical significance between SSc-PAH and controls. p value < 0.05

[†]Statistical significance between other CTD-PAH and controls. p value < 0.05

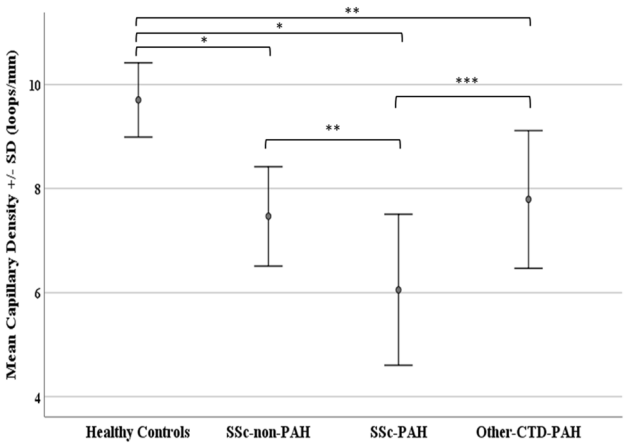

Fig. 1 Capillary density (loops/mm). Error bars represent the mean capillary density ± standard deviation (SD) in healthy controls (9.7 ± 0.7 loops/mm), patients with systemic sclerosis without pulmonary arterial hypertension (SSc-non-PAH) (7.5 ± 0.9 loops/mm), patients with systemic sclerosis associated pulmonary arterial hypertension (SSc-PAH) (6.1 ± 1.4 loops/mm) and patients with pulmonary arterial hypertension due to other connective tissue diseases (other-CTD-PAH) (7.8 ± 1.3 loops/mm). Difference in capillary density was significant among all groups ($p < 0.001$). In detail, patients with SSc-non-PAH and SSc-PAH presented significantly lower capillary density compared to healthy controls (*$p < 0.001$). Patients with other CTD-PAH presented lower capillary density than healthy controls (**$p < 0.01$). In addition, patients with SSc-PAH presented significantly lower capillary density compared to SSc-non-PAH subjects (**$p < 0.01$) and to other-CTD-PAH individuals (***$p = 0.02$). No statistically significant difference in capillary density was found between other CTD-PAH and SSc-non-PAH subjects

significant capillary shape and architecture abnormalities were spotted in SSc-PAH patients compared to healthy controls, whereas patients with other-CTD-PAH and SSc-non-PAH patients did not present increased abnormal or disorganized capillaries in comparison to controls (Table 2). Figure 2 depicts capillaroscopic images of various CTD-PAH patients and control subjects.

In SSc-PAH group, the majority of patients presented a worse scleroderma pattern (3 patients presented the early pattern, 6 patients the active and 4 the late pattern) compared to SSc-non-PAH subjects ($p = 0.01$) (Supplementary File). The other CTD-PAH individuals presented a non-specific NVC pattern apart from the patient with MCTD that had an active scleroderma pattern. According to the semi-quantitative classification, the majority of CTD-PAH patients (83.3%) and SSc-non-PAH subjects (92.8%) presented mild capillaroscopic changes (score: 1), while the rest of them had more severe changes (score: 2). None of the other-CTD-PAH group presented a severe NVC score (Supplementary File). A kappa coefficient value of 0.79 indicated a good inter-observer agreement in the evaluation of the semi-quantitative rating scale. Severity score was significantly associated with the presence of anti-Scl-70 antibodies in the total SSc cohort (OR 22, 95% CI 1.3, 362.1, $p = 0.03$), while no significant association was found with the presence of ACA (OR 0.1, 95% CI 0.1, 14.1, $p = 0.9$) and ANA antibodies (OR 2.7, 95% CI 0.24, 30.5, $p = 0.5$), respectively.

Correlations between capillaroscopic characteristics and markers of renal and cardiac function

eGFR was positively correlated with capillary density in CTD-PAH patients [$r = 0.63$, $B = 0.04$, 95% CI (0.01, 0.06), $p = 0.007$] in univariate regression analysis (Fig. 3). In multivariable analysis, including age and DLCO% as potential confounders, eGFR significantly predicted capillary density [$r = 0.73$, $B = 0.04$, 95% CI (0.01, 0.07), $p = 0.006$], while age and DLCO% were not significantly associated with capillary density (Supplementary File, Table 2). In SSc-PAH group, capillary loop diameter was positively correlated to cardiac index [$r = 0.61$, $B = 9.6$, 95% CI (1.4, 17.9), $p = 0.02$] (Fig. 4). In addition, DLCO% was positively correlated with capillary density in the patient cohort, including CTD-PAH and SSc-non-PAH individuals [$r = 0.50$, $B = 0.03$, 95% CI (0.007, 0.054), $p = 0.01$] that could render this variable as a potential confounder regarding differences in capillary density between the groups (Supplementary File). On the other hand, age was not found to be a confounding factor in terms of between-groups differences in capillary density (Supplementary File). No other biochemical, functional, or hemodynamic variables were correlated with capillary features in the total CTD-PAH population (Supplementary File, Table 2).

Discussion

The main finding of our study is the demonstration of peripheral microvascular impairment assessed by NVC among patients with PAH associated with various CTDs. In particular, CTD-PAH patients presented both reduced capillary density and increased capillary dimensions compared to controls, while microhemorrhages, thrombi, shape abnormalities and capillary disorganization were also observed. As expected, NVC changes were more prominent in SSc-PAH, however, specific microvascular abnormalities indicative of PAH namely reduced capillary density and increased loop width [17] were also observed in patients with PAH due to other CTDs. Overall, this study reports NVC microvascular alterations in a variety of CTD subsets complicated with PAH, indicating that disturbed structure and function of peripheral microcirculation may be common across the whole spectrum of CTD-PAH and not only within SSc-PAH.

The results of this study suggest that all types of CTD-PAH result in peripheral vasculopathy, despite partially different pathogenetic mechanisms in the development of

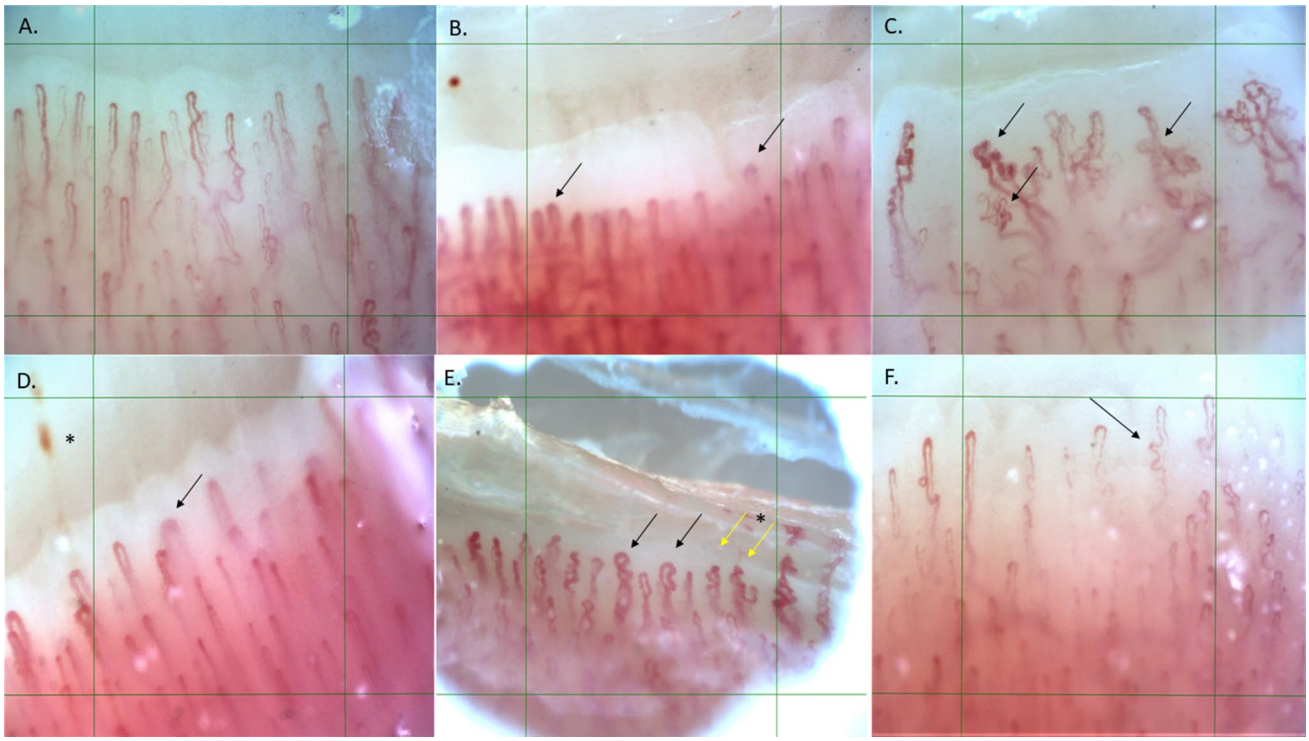

Fig. 2 Nailfold videocapillaroscopic changes in patients with various types of CTD-PAH. **a** Healthy control; normal capillary density (9 loops/mm), hairpin-shaped capillaries with normal loop width. **b** Systemic sclerosis without PAH (SSc-non-PAH); early scleroderma pattern. Normal capillary density (9 loops/mm), irregularly enlarged capillaries (arrows). **c** PAH associated with systemic sclerosis (SSc-PAH); late scleroderma pattern. Reduced capillary density (6 capillary loops/mm), disorganized and abnormal capillaries (arrows). **d** PAH associated with mixed connective tissue disease (MCTD-PAH); early scleroderma pattern with mildly reduced capillary density (7 capillary loops/mm) and giant capillaries (arrow). Out of grid pattern, there is a microhemorrhage (asterisk). **e** PAH associated with rheumatoid arthritis (RA-PAH); normal capillary density. Irregularly enlarged (black arrows), abnormal capillaries (yellow arrows) and microhemorrhage (asterisk). **f** PAH associated with systemic lupus erythematosus (SLE-PAH); reduced capillary density (6 loops/mm). Irregularly enlarged capillary (arrow). *PAH* pulmonary arterial hypertension, *CTD* connective tissue disease. Grid pattern represents area of 1 mm^2. Magnification ×200

PAH. For example, fibrous remodeling leading to obliterate pulmonary vasculopathy constitute the main process in SSc, whereas vasculitis and thrombosis are considered to have a significant impact in SLE and MCTD associated PAH [29]. However, autoimmune activation and systemic inflammation which are common in CTD appear to contribute to the presence of peripheral microangiopathy as suggested by the documented association between NVC abnormalities and anti-topoisomerase antibodies. Vascular endothelial growth factor (VEGF) and proinflammatory cytokines are likely mediators of chronic hypoxia-driven pulmonary and peripheral vascular remodeling, by mobilizing endothelial progenitor cells (EPCs) [30]. Reduced circulating EPCs despite VEGF stimulus in SSc have been linked with capillary loss and abnormal NVC patterns [31]. Taking all together, deficient vasculogenesis and insufficient endothelial repair may contribute to the capillary rarefaction [32], observed among CTD-PAH. The strong correlation between eGFR—a marker of renal vascular dysfunction—and reduced capillary density similarly to what occurs in patients with chronic kidney disease [33] further supports the presence of a widespread vasculopathy in patients with CTD-PAH. In the context of SSc, reduced eGFR has been also linked with worse NVC pattern in patients without known chronic kidney disease [34].

The majority of existing NVC studies until today have focused on systemic microvascular changes in SSc-PAH individuals by demonstrating a significant reduction in capillary density in parallel with an increase in capillary loop width compared to SSc controls, both of which have been correlated with hemodynamic severity such as mPAP [13, 16, 35]. In addition, the presence of giant capillaries [13], neoangiogenesis, and more severe NVC pattern [13, 36] were observed in SSc-PAH patients compared to SSc patients without PAH. Our study confirms previous findings [40], by demonstrating worse NVC features in SSc-PAH compared to SSc-non-PAH individuals, while a positive correlation between cardiac index and capillary loop width was also detected. SSc-PAH patients with a preserved cardiac index may present with widened capillaries as a marker of

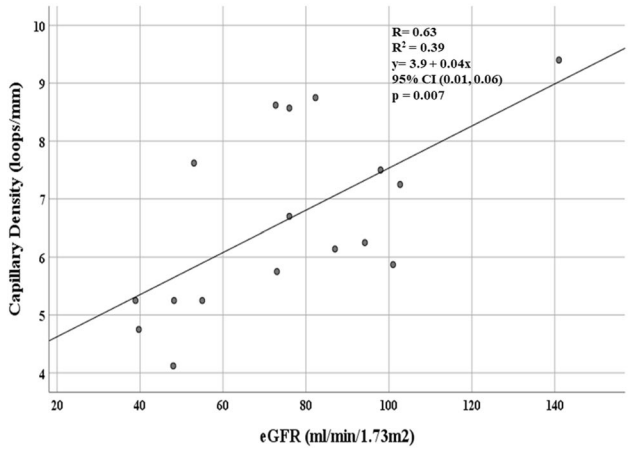

Fig. 3 Scatter plot depicting linear correlation between capillary density and renal function in patients with CTD-PAH. Positive linear correlation between capillary density (loops/mm) and estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) in patients with CTD-PAH. Univariate linear regression analysis was used. R-coefficient and linear equations with 95% confidence intervals (CI) are depicted. A p value < 0.05 is considered statistically significant. *CTD-PAH* pulmonary arterial hypertension associated with connective tissue disease, *eGFR* estimated glomerular filtration rate

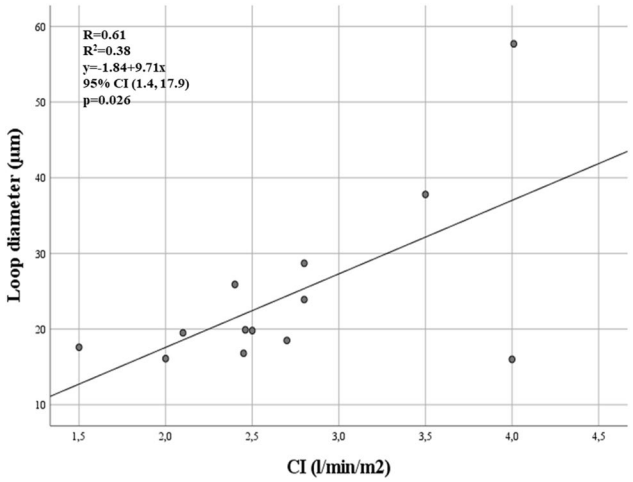

Fig. 4 Scatter plot depicting linear correlation between loop diameter and cardiac index in patients with SSc-PAH. Positive linear correlation between loop diameter (µm) and cardiac index (l/min/1.73m^2) assessed with right heart catheterization in patients with SSc-PAH. Univariate linear regression analysis was used. R-coefficient and linear equations with 95% confidence intervals (CI) are depicted. A p value < 0.05 is considered statistically significant. *SSc-PAH* pulmonary arterial hypertension associated with systemic sclerosis

less severe scleroderma pattern that tend to disappear with disease progression [37] and reduction of cardiac index.

In addition to NVC changes in SSc-PAH patients, our study reports on capillaroscopic characteristics presented in a small heterogenous group of patients with PAH associated to various CTDs. In particular, it demonstrates the presence of reduced capillary density, avascular areas and increased capillary dimensions with irregularly enlarged capillaries that range between the spectrum of NVC alterations in SSc-PAH and SSc-non-PAH/healthy controls. Furthermore, all patients with other CTD-PAH presented abnormal NVC features as detected by semi-quantitative assessment. So far, Donnarumma et al. examined 16 patients with SLE-PAH and 44 with SLE without PAH and found that patients with SLE-PAH had significantly dilated capillaries and more avascular areas than SLE controls, that are in accordance with our findings [14]. In addition, scleroderma pattern was found to be correlated with SLE-PAH [14]. To our knowledge, no further data exist related to microvascular changes in patients with CTD-PAH not associated with SSc.

The main limitation of our study is the small sample size, which could explain the lack of power to detect a significant association between capillaroscopic and functional or hemodynamic markers of cardiac dysfunction and also to detect a significant difference between groups (excluding healthy controls) regarding giant capillaries, microhemorrhages and capillary edema. The structured study protocol, i.e., hemodynamic and capillaroscopic data recorded within the same time interval, has considerably contributed to the low number of participants. Another limitation is that the majority of patients have been receiving PAH-specific therapy which could be a confounding factor for NVC changes. Furthermore, the fact that SSc-PAH individuals had reduced DLCO% compared to SSc-non-PAH group, as a marker of lung disease progression, could act as another confounding factor. Nevertheless, previous studies have established associations between DLCO and NVC alterations is SSc patients [36, 38], irrespective of the presence of PAH as occurs in our population. In addition, the absence of controls matched for the underlying CTD with patients with other CTD-PAH could have underpowered the detection of more severe NVC characteristics in this population.

The novelty of our study compared to previous ones lies in the recruitment of PAH patients across the whole spectrum of CTDs. Furthermore, NVC was conducted in all fingers except thumbs and two adjacent images were acquired from each finger according to the updated EULAR recommendations [26]. In addition, qualitative and semi-quantitative assessment was performed based on a validated algorithm proposed by Smith et al., which facilitates parameters that can be reliably measured by two trained examiners with a good inter-observer agreement [26, 38, 39].

Conclusion

This study demonstrated significant NVC microvascular changes in patients with SSc-PAH and PAH associated with other types of CTD suggestive of an impaired peripheral

microcirculation parallel to pulmonary vasculopathy in a wider spectrum of CTD-PAH. The strong positive correlation between renal function and capillary density is indicative of the multisystemic microvascular involvement in CTD-PAH. Larger prospective well-designed studies are warranted to confirm our preliminary results.

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Author contributions AA performed the NVC examination, stored and coded the images. AA collected, statistically analyzed and interpreted all data and drafted the manuscript. ET and EP analyzed the NVC images in a blinded manner. GG performed the right heart catheterization and the transthoracic echocardiography. AA, GG and TD conceived the idea, designed the study and critically revised the manuscript. AB, AG and HK critically revised the manuscript for important intellectual content. All the authors read and approved the final manuscript.

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Availability of data and material All data of this study are available upon request.

Declarations

Conflict of interest AA is the recipient of the International Training and Research Fellowship EMAH Stiftung Karla Voellm, Krefeld, Germany. The rest of the authors declare no conflicts of interest other than the grant received for this research.

Ethics approval The study received approval from the Aristotle University of Thessaloniki Ethics Committee (protocol number 264) and was performed according to the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of the images in Fig. 2a–f.

References

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M et al (2019) Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Res J. https://doi.org/10.1183/13993003.01913-2018
2. Yang X, Mardekian J, Sanders KN, Mychaskiw MA, Thomas J 3rd (2013) Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a systematic review of the literature. Clin Rheumatol 32(10):1519–1531. https://doi.org/10.1007/s10067-013-2307-2
3. Rubio-Rivas M, Homs NA, Cuartero D, Corbella X (2021) The prevalence and incidence rate of pulmonary arterial hypertension in systemic sclerosis: systematic review and meta-analysis. Autoimmun Rev 20(1):102713. https://doi.org/10.1016/j.autrev.2020.102713
4. Galiè N, Manes A, Farahani KV, Pelino F, Palazzini M, Negro L et al (2016) Pulmonary arterial hypertension associated to connective tissue diseases. Lupus 14(9):713–717. https://doi.org/10.1191/0961203305lu2206oa
5. Shahane A (2013) Pulmonary hypertension in rheumatic diseases: epidemiology and pathogenesis. Rheumatol Int 33(7):1655–1667. https://doi.org/10.1007/s00296-012-2659-y
6. Dimitroulas T, Giannakoulas G, Karvounis H, Settas L, Kitas GD (2011) Biomarkers in systemic sclerosis-related pulmonary arterial hypertension. Curr Vasc Pharmacol 9(2):213–219. https://doi.org/10.2174/157016111794519381
7. Soulaidopoulos S, Pagkopoulou E, Katsiki N, Triantafyllidou E, Karagiannis A, Garyfallos A et al (2019) Arterial stiffness correlates with progressive nailfold capillary microscopic changes in systemic sclerosis: results from a cross-sectional study. Arthritis Res Ther. https://doi.org/10.1186/s13075-019-2051-3
8. Takahashi T, Asano Y, Amiya E, Hatano M, Tamaki Z, Takata M et al (2013) Clinical correlation of brachial artery flow-mediated dilation in patients with systemic sclerosis. Mod Rheumatol 24(1):106–111. https://doi.org/10.3109/14397595.2013.854064
9. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al (2013) 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 65(11):2737–2747. https://doi.org/10.1002/art.38098
10. Repa A, Avgoustidis N, Kougkas N, Bertsias G, Zafiriou M, Sidiropoulos P (2019) Nailfold videocapillaroscopy as a candidate biomarker for organ involvement and prognosis in patients with systemic sclerosis. Mediterr J Rheumatol 30(1):48–50. https://doi.org/10.31138/mjr.30.1.48
11. Smith V, Thevissen K, Trombetta AC, Pizzorni C, Ruaro B, Piette Y et al (2016) Nailfold capillaroscopy and clinical applications in systemic sclerosis. Microcirculation 23(5):364–372. https://doi.org/10.1111/micc.12281
12. Soulaidopoulos S, Triantafyllidou E, Garyfallos A, Kitas GD, Dimitroulas T (2017) The role of nailfold capillaroscopy in the assessment of internal organ involvement in systemic sclerosis: a critical review. Autoimmun Rev 16(8):787–795. https://doi.org/10.1016/j.autrev.2017.05.019
13. Corrado A, Correale M, Mansueto N, Monaco I, Carriero A, Mele A et al (2017) Nailfold capillaroscopic changes in patients with idiopathic pulmonary arterial hypertension and systemic sclerosis-related pulmonary arterial hypertension. Microvasc Res 114:46–51. https://doi.org/10.1016/j.mvr.2017.06.005
14. Donnarumma JFS, Ferreira EVM, Ota-Arakaki J, Kayser C (2019) Nailfold capillaroscopy as a risk factor for pulmonary arterial hypertension in systemic lupus erythematosus patients. Adv Rheumatol 59(1):1. https://doi.org/10.1186/s42358-018-0045-5
15. Greidinger EL, Gaine SP, Wise RA, Boling C, Housten-Harris T, Wigley FM (2001) Primary pulmonary hypertension is not associated with scleroderma-like changes in nailfold capillaries. Chest 120(3):796–800. https://doi.org/10.1378/chest.120.3.796
16. Hofstee HM, Vonk Noordegraaf A, Voskuyl AE, Dijkmans BA, Postmus PE, Smulders YM et al (2009) Nailfold capillary density is associated with the presence and severity of pulmonary arterial hypertension in systemic sclerosis. Ann Rheum Dis 68(2):191–195. https://doi.org/10.1136/ard.2007.087353
17. Arvanitaki A, Giannakoulas G, Triantafyllidou E, Karvounis H, Garyfallos A, Kitas G et al (2021) Nailfold videocapillaroscopy: a novel possible surrogate marker for the evaluation of peripheral microangiopathy in pulmonary arterial hypertension. Scand J Rheumatol 50(2):85–94. https://doi.org/10.1080/03009742.2020.1786854

18. Arvanitaki A, Giannakoulas G, Triantafyllidou E, Feloukidis C, Boutou AK, Garyfallos A et al (2021) Peripheral microangiopathy in precapillary pulmonary hypertension: a nailfold video capillaroscopy prospective study. Respir Res 21:22(1):27. https://doi.org/10.1186/s12931-021-01622-1
19. Arvanitaki A, Giannakoulas G, Triantafyllidou E, Karvounis H, Dimitroulas T (2020) Peripheral microangiopathy in patients with precapillary pulmonary hypertension: correlation with cardiac function and patients' functional capacity. Study design and rationale. Mediterr J Rheumatol. 31(3):369–373. https://doi.org/10.31138/mjr.31.3.369
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP et al (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 370(9596):1453–1457. https://doi.org/10.1016/S0140-6736(07)61602-X
21. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al (2015) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 46(4):903–975. https://doi.org/10.1183/13993003.01032-2015
22. Hofstee HM, Serne EH, Roberts C, Hesselstrand R, Scheja A, Moore TL et al (2012) A multicentre study on the reliability of qualitative and quantitative nail-fold video capillaroscopy assessment. Rheumatology 51(4):749–755. https://doi.org/10.1093/rheumatology/ker403
23. Etehad Tavakol M, Fatemi A, Karbalaie A, Emrani Z, Erlandsson B-E (2015) Nailfold capillaroscopy in rheumatic diseases: which parameters should be evaluated? Biomed Res Int 2015:1–17. https://doi.org/10.1155/2015/974530
24. Ingegnoli F, Gualtierotti R, Lubatti C, Zahalkova L, Meani L, Boracchi P et al (2009) Feasibility of different capillaroscopic measures for identifying nailfold microvascular alterations. Semin Arthritis Rheum 38(4):289–295. https://doi.org/10.1016/j.semarthrit.2007.10.008
25. Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP et al (2020) Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev 19(3):102458 https://doi.org/10.1016/j.autrev.2020.102458
26. Smith V, Vanhaecke A, Herrick AL, Distler O, Guerra MG, Denton CP et al (2019) Fast track algorithm: how to differentiate a "scleroderma pattern" from a "non-scleroderma pattern." Autoimmun Rev 18(11):102394. https://doi.org/10.1016/j.autrev.2019.102394
27. Smith V, Pizzorni C, De Keyser F, Decuman S, Van Praet JT, Deschepper E et al (2010) Reliability of the qualitative and semi-quantitative nailfold videocapillaroscopy assessment in a systemic sclerosis cohort: a two-centre study. Ann Rheum Dis 69(6):1092–1096. https://doi.org/10.1136/ard.2009.115568
28. Sulli A, Secchi ME, Pizzorni C, Cutolo M (2008) Scoring the nailfold microvascular changes during the capillaroscopic analysis in systemic sclerosis patients. Ann Rheum Dis 67(6):885–887. https://doi.org/10.1136/ard.2007.079756
29. Jais X, Launay D, Yaici A, Le Pavec J, Tchérakian C, Sitbon O et al (2008) Immunosuppressive therapy in lupus- and mixed connective tissue disease–associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. Arthritis Rheum 58(2):521–531. https://doi.org/10.1002/art.23303
30. Kylhammar D, Hesselstrand R, Nielsen S, Scheele C, Radegran G (2018) Angiogenic and inflammatory biomarkers for screening and follow-up in patients with pulmonary arterial hypertension. Scand J Rheumatol 47(4):319–324. https://doi.org/10.1080/03009742.2017.1378714
31. Nevskaya T, Bykovskaia S, Lyssuk E, Shakhov I, Zaprjagaeva M, Mach E et al (2008) Circulating endothelial progenitor cells in systemic sclerosis: relation to impaired angiogenesis and cardiovascular manifestations. Clin Exp Rheumatol 26(3):421–429
32. Avouac J, Vallucci M, Smith V, Senet P, Ruiz B, Sulli A et al (2013) Correlations between angiogenic factors and capillaroscopic patterns in systemic sclerosis. Arthritis Res Ther 15(2):R55. https://doi.org/10.1186/ar4217
33. Schoina M, Loutradis C, Memmos E, Dimitroulas T, Pagkopoulou E, Doumas M et al (2021) Microcirculatory function deteriorates with advancing stages of chronic kidney disease independently of arterial stiffness and atherosclerosis. Hypertens Res 44(2):179–187. https://doi.org/10.1038/s41440-020-0525-y
34. Gigante A, Barbano B, Granata G, Quarta S, Amoroso A, Salsano F et al (2016) Evaluation of estimated glomerular filtration rate and clinical variables in systemic sclerosis patients. Clin Nephrol 85(6):326–331. https://doi.org/10.5414/CN108580
35. Riccieri V, Vasile M, Iannace N, Stefanantoni K, Sciarra I, Vizza CD et al (2013) Systemic sclerosis patients with and without pulmonary arterial hypertension: a nailfold capillaroscopy study. Rheumatology 52(8):1525–1528. https://doi.org/10.1093/rheumatology/ket168
36. Guillén-Del-Castillo A, Simeón-Aznar CP, Callejas-Moraga EL, Tolosa-Vilella C, Alonso-Vila S, Fonollosa-Pla V et al (2018) Quantitative videocapillaroscopy correlates with functional respiratory parameters: a clue for vasculopathy as a pathogenic mechanism for lung injury in systemic sclerosis. Arthritis Res Ther. https://doi.org/10.1186/s13075-018-1775-9
37. Avouac J, Lepri G, Smith V, Toniolo E, Hurabielle C, Vallet A et al (2017) Sequential nailfold videocapillaroscopy examinations have responsiveness to detect organ progression in systemic sclerosis. Semin Arthritis Rheum 47(1):86–94. https://doi.org/10.1016/j.semarthrit.2017.02.006
38. Caetano J, Paula FS, Amaral M, Oliveira S, Alves JD (2019) Nailfold video capillaroscopy changes are associated with the presence and severity of systemic sclerosis-related interstitial lung disease. J Clin Rheumatol 25(3):e12–e15. https://doi.org/10.1097/RHU.0000000000000815
39. Smith V, Beeckman S, Herrick AL, Decuman S, Deschepper E, De Keyser F et al (2016) An EULAR study group pilot study on reliability of simple capillaroscopic definitions to describe capillary morphology in rheumatic diseases. Rheumatology 55(5):883–890. https://doi.org/10.1093/rheumatology/kev441
40. Minopoulou I, Theodorakopoulou M, Boutou A, Arvanitaki A, Pitsiou G, Doumas M, Sarafidis P, Dimitroulas T (2021) Nailfold capillaroscopy in systemic sclerosis patients with and without-pulmonary arterial hypertension: a systematic review and meta-analysis. J Clin Med 10(7):1528.https://doi.org/10.3390/jcm10071528