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ORIGINAL ARTICLE

Peripheral microcirculatory abnormalities are associated with cardiovascular risk in systemic sclerosis: a nailfold video capillaroscopy study

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Abstract

Introduction Microvascular dysfunction is the key element in the pathogenesis of systemic sclerosis (SSc), whereas the contribution of large and medium size vessel abnormalities is yet to be established. The aim of the present study is to assess the association between micro- and macrovascular function by utilizing a broad spectrum of assessments of vascular performance.

Methods We included consecutive, consenting SSc patients who underwent nailfold video capillaroscopy (NVC) for microcirculation evaluation. Peripheral and central systolic and diastolic blood pressure, carotid intima-media thickness (cIMT), aortic augmentation index (AIx) corrected for a heart rate of 75 beats per minute (AIx-75), and carotid-femoral pulse wave velocity (PWV) were also performed to assess macrovascular function. Cardiovascular risk disease (CVD) algorithms were also calculated and included in the analysis.

Results A total of 81 patients (6 males) were studied with mean age 55.44 ± 13.40 years. Reduced capillary density was inversely correlated with arterial stiffness (Alx-75) and augmentation pressure ($r = -0.262$, $p = 0.018$, and $r = -0.249$, $p = 0.025$ respectively). Alx was significantly lower in the early compared to late pattern (28.24 ± 11.75 vs 35.63 ± 10.47, $p = 0.036$). A significant trend was found among NVC patterns with Alx-75 values being higher with the progression of microangiopathy towards the "late" group (26.36 ± 10.90 vs 30.81 ± 11.59 vs 35.21 ± 7.90, $p = 0.027$ for trend). Similarly, Framingham risk score and Atherosclerotic Cardiovascular Disease score were progressively higher across the worsening NVC patterns (4.10 ± 4.13 vs 2.99 ± 2.72 vs 6.36 ± 5.65, $p = 0.023$, and 6.99 ± 7.18 vs 5.63 ± 4.41 vs 12.09 ± 9.90, $p = 0.019$, respectively, for trends). Finally, QRISK3 (10-year cardiovascular disease risk) and ASCVD (Atherosclerotic Cardiovascular Disease) scores were inversely correlated with the number of capillaries ($r = -0.231$, $p = 0.048$, and $r = -0.260$, $p = 0.038$ respectively).

Conclusion These data suggest that CVD risk scores and macrovascular parameters are strongly correlated with microvasculopathy in patients with SSc.

Key Points

- *Microangiopathy is the hallmark of SSc, but the relationship between subclinical atherosclerosis and small vessel disease remains unknown.*
- *Arterial stiffening and CVD risk scores are positively associated with the degree of progression of peripheral microvasculopathy assessed with NVC.*
- *The results of the study suggest an association between NVC abnormalities and higher CVD risk in SSc patients.*

Keywords Atherosclerosis · Cardiovascular disease · Nailfold video capillaroscopy · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a rare systemic connective tissue disease characterized by microvascular damage, immune dysregulation, and extensive skin and internal

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organ fibrosis [1]. The course and prognosis of the SSc is mainly determined by the extent and severity of involvement of visceral organs and in particular by cardiopulmonary complications that represent the leading cause of death in this population [2, 3]. Impairment of the microcirculation represents the primary event that progressively stimulates the fibrotic process and results in typical clinical manifestations such as Raynaud's syndrome, digital ulcers, pulmonary arterial hypertension, and renal crisis [4].

Besides the well-described microcirculatory injury, macrovascular, atherosclerotic disease has emerged as a significant component of generalized vascular pathology [5, 6] which may—at least partially—account for the increased rate of cardiovascular (CV) events reported in patients with SSc [7]. In particular, a number of studies have shown functional and morphological abnormalities of large and medium size vessels assessed by aortic augmentation index (AIx-75), carotid-femoral pulse wave velocity (PWV) [8, 9], and carotid intima-media thickening (cIMT) [10]. The evidence for the presence of accelerated atherosclerosis in SSc is further supported by recent comparative studies indicating similar CV comorbidity burden defined as the occurrence of stroke and myocardial infarction [11] as well as a comparable degree of subclinical atherosclerosis assessed by cIMT and Aix-75 between SSc and rheumatoid arthritis [12]—the prototypic and best-studied systemic rheumatic disorder with regard to high CV risk.

Nailfold video capillaroscopy (NVC) is a non-invasive, easily reproducible imaging study of capillary circulation. NVC is a well-documented, accepted diagnostic technique for microcirculation evaluation, as well as the identification of microvascular invasion that characterizes SSc and other rheumatic diseases [13, 14] and it is currently included in the latest classification criteria for SSc diagnosis [15]. Specific capillary vascular lesions observed in SSc that form a characteristic morphological pattern known as the "scleroderma pattern" were first described four decades ago [16]. Over the last years, the implications of NVC have expanded beyond the diagnostic evaluation of Raynaud's phenomenon as numerous associations between microvascular alterations and complications of SSc have been established [10], to the point that NVC patterns are considered as potential surrogate markers of disease severity [17]. In the context of atherosclerosis, a handful of small studies have correlated NVC microangiopathic abnormalities with indices of macrovascular disease such as brachial artery endothelial-dependent flow-mediated dilation [18], arterial stiffness [19, 20], and aortic root dilatation [21] in SSc individuals suggesting a possible connection between theoretically distinct aspects of vascular involvement in SSc. However, this question has not been addressed in large studies.

The aim of this study was to examine the relationship between NVC parameters and major parameters of macrovascular function in a well-defined cohort of SSc patients. The association between microcirculatory changes and CV risk algorithms was also assessed.

Materials and methods

Study participants and inclusion/exclusion criteria

Consecutive SSc patients attending the Scleroderma Clinic of the Fourth Department of Internal Medicine, Hippokration General Hospital, Thessaloniki, Greece, between March 2018 and September 2020 were screened for the study. All patients met the revised EULAR/ACR criteria for the diagnosis of SSc [15]. Exclusion criteria included past diagnosis of cardiovascular disease (CVD) defined as coronary heart disease, stroke or peripheral vascular disease, diabetes mellitus, as well as patients with carotid artery surgical procedures. The study received ethics approval from the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki, and written informed consent was obtained from all participants according to the Declaration of Helsinki.

Protocol overview

All participants underwent a thorough physical examination and demographic data were collected by a questionnaire. Complete medical history was also recorded which included the duration of the disease; diagnosis of pulmonary hypertension, pulmonary fibrosis, or esophageal motility disorders, as documented by imaging or endoscopic examination, respectively; medication; and traditional CV risk factors. Various hematological and biochemical laboratory parameters such as routine biochemistry and hematology, lipid and bone profile tests, inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), immunological markers such as antinuclear antibodies, anti-centromere antibodies, and anti-topoisomerase II antibodies were tested.

For reason of completeness, we estimated CV risk score using Framingham Risk Score (coronary heart disease risk at 10 years) [22], QRISK3 (the most recent version of QRISK used for prediction of cardiovascular disease) [23], and Atherosclerotic Cardiovascular Disease (ASCVD) algorithm (10-year risk of heart disease or stroke) [24]. Based on the data, their risk scores were calculated. All calculators provided the risk score in numeric values.

Protocol procedures and assessments

BP measurement

Blood pressure was recorded according to 2018 ESC/ESH Guidelines for the management of arterial hypertension [25]. All patients were seated comfortably in a quiet environment for 5 min before beginning BP measurements. Three BP measurements were recorded, 1–2 min apart, and additional measurements only if the first two readings differed by > 10 mmHg. BP was recorded as the average of the last two BP readings. The presence of an auscultatory gap during manual BP measurement—the temporary disappearance of the Korotkoff sounds during cuff deflation—may lead to a potentially important underestimation of SBP if undetected. Thus, electronic oscillometric BP is preferred in SSc patients [26]. BP was measured using Omron HBP-1320, which is validated for professional use [27].

Nailfold video capillaroscopy

The NVC with an Optilia Digital Capillaroscope and a × 200 contact lens was used in all patients. Photos were collected, registered, and analyzed with the OptiPix Capillaroscopy software system. Prior to performing the test, patients were placed in a quiet environment at a temperature of between 20 and 25 °C. For better image analysis, a drop of cedar oil was placed on the fingernails of each finger prior to observation. The examination was performed on all participants by the same physician and the pathological morphological findings were classified in one of the following qualitative patterns: early, active, and late NVC pattern [28]. The "early" pattern was characterized by a few enlarged or giant capillaries, elongation or twisting of capillary brackets without apparent capillary loss, and relatively well-preserved capillary distribution; the "active" pattern was characterized by numerous large capillary vessels, mildly disturbed capillary architecture, and moderate capillary loss; the "late" type was characterized by severe capillary loss with extensive vascular desertification, little or no capillary vessels, and disruption of normal capillary architecture and capillary network [29, 30]. These patterns are supposed to reflect progressing vasculopathy, with the "early" one characterizing the incipient vascular changes, and the "active" and "late" patterns mirroring the extensive capillary disorganization that characterizes the later fibrotic stages of SSc [31]. NVC parameters measured were capillary density (number of capillaries per 1 mm in the distal row of each finger [32]), giant capillaries (homogeneously enlarged capillaries > 50 μm), enlarged capillaries (> 20 μm and ≤ 50 μm), microbleeding, edema, avascular areas (the normal range adopted was 9 capillaries per linear millimeter), ramified capillaries, and bushy and tortuous capillaries [13]. The mean of each capillaroscopic feature was calculated from the sum of consecutive images for each finger. Subsequently, the average values from eight fingers was added together and divided by the number of studied fingers [13]. Furthermore, the mean capillaroscopic skin ulcer risk index (CSURI), according to the formula D × M:N2 (D maximum diameter of giant capillaries, M number of giant capillaries, and N total number of capillaries in the distal row), was calculated for each participant. The images were reviewed by two independent NVC experts (EP and ET) with the latter being blinded to clinical data. The analysis did not reveal any inter-observer variability.

Carotid intima-media thickness

cIMT measurement of 2 common carotid arteries was performed with a 2D ultrasound device (GE Healthcare Ultrasound, Vivid S5, 8L-RS probe, USA), in the common carotid artery between the middle and inner surface of the right and left artery wall, which is represented by a dense double line pattern, by an operator blinded to the NVC findings. The examination and measurement techniques were applied according to standardized protocols [33].

Arterial stiffness

The patients were referred to the Arterial Hypertension Laboratory of the Second Department of the Aristotle University of Thessaloniki, where tonometric measurement of arterial stiffness indices was carried out. Office arterial stiffness parameters were evaluated by performing applanation tonometry with the use of a sensitive pencil-type tonometer (SPT-301, Millar Instruments) attached to the SphygmoCor device (AtCor, Sydney, Australia). Oscillometric evaluation of systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the level of brachial artery, averaged from two measurements per occasion, was used for the calibration of pulse waveforms. Pulse wave analysis was performed from radial artery recordings with the use of a generalized radial-to-aortic transfer function, which provides an accurate estimate of the central arterial pressure waveform. Aortic PWV was measured by recordings of pulse waveforms at the carotid and femoral arteries. Pulse waveforms were referenced to a concurrently recorded ECG, and pulse wave transit time between the subsequent recording sites was calculated from the SphygmoCor software, according to the foot-to-foot time difference between carotid-femoral waveforms. Pulse waveforms were recorder over 10 consecutive heartbeats to cover a complete respiratory cycle. The average of three valid measurements was used in the analysis [34, 35].

Statistical analysis

Statistical analysis was performed with SPSS for Windows (version 22.0 IBM Corp: Armonk, NY, USA). Categorical variables are presented with relevant frequencies and percentages (n, %) and continuous variables are presented as mean values ± standard deviation (SD) or median [interquartile range] according to the normality. The normality of distribution was tested with the Kolmogorov–Smirnov or the Shapiro–Wilk tests. Comparisons for continuous variables were performed with the Student *t*-test or the Mann–Whitney *U* test, according to the normality of the distribution. The chi-square or the Fisher's exact test was used for comparisons between categorical variables. Bivariate correlations between continuous parameters were calculated with the Pearson's *r* or the Spearman's rank correlation coefficient. *p* values ≤ 0.05 (two-tailed) were considered statistically significant for all comparisons. Adjustment for confounders assumed to influence the reported associations, namely age, arterial hypertension, and antihypertensive treatment, was conducted via partial correlations. Next, factors associated with the outcome at the $p < 0.2$ level in univariate analyses were included in a multivariate model as potential confounders. Inter-observer variability for the NVC findings was compared using the Bland–Altman method and for NVC patterns using kappa statistics. Multiple comparisons correction for the correlation analysis was performed using the Benjamini and Hochberg method and a false discovery rate of 50%.

Results

Patient characteristics

A total of 81 SSc patients (6 males) with mean age 55.44 ± 13.40 years were included in the study. Demographic, clinical, and laboratory characteristics of the study population are presented in Table 1.

Table 1 Baseline characteristics of the study participants

Parameter	Values
N	81
Age (years)	55.44 ± 13.40
Male (n, %)	6 (7.4%)
Weight (kg)	64.88 ± 10.70
Height (m)	1.62 ± 0.06
BMI (m^2)	24.56 [3.64]
Smoking (n, %)	18 (22.2%)
Hypertension (n, %)	24 (29.6%)
Raynaud (n, %)	76 (93.8%)
Ulcers (n, %)	26 (32.1%)
Pulmonary fibrosis (n, %)	27 (33.3%)
Pulmonary hypertension (n, %)	12 (14.8%)
Esophageal involvement (n, %)	29 (35.8%)
Dyslipidemia (n, %)	7 (8.6%)
Steroids currently (n, %)	30 (37.0%)
Rituximab (n, %)	8 (9.9%)
Cyclophosphamide (n, %)	3 (3.7%)
Methotrexate (n, %)	24 (29.6%)
Mycophenolate (n, %)	25 (30.9%)
Plaquenil (n, %)	16 (19.8%)
Azathioprine (n, %)	7 (8.6%)
Tocilizumab (n, %)	2 (2.5%)
Antihypertensive (any) (n, %)	50 (61.7%)
ACEI (n, %)	11 (13.6%)
ARB (n, %)	2 (2.5%)
Diuretics (n, %)	6 (7.4%)
CCB (n, %)	39 (48.1%)
B–blocker (n, %)	1 (1.2%)
ERAs (n, %)	22 (27.2%)
Statins (n, %)	7 (8.6%)
ANA + (n, %)	70 (86.4%)
ACA + (n, %)	21 (25.9%)
Scl-70 + (n, %)	28 (34.6%)
ESR (mm/h)	17.00 [18.00]
CRP (mg/dl)	0.71 [4.15]
Hemoglobin (gr/dl)	12.80 [1.50]
Uric acid (mg %)	4.00 [1.87]

Abbreviations: *ACEI*, angiotensin-converting enzyme inhibitors; *ARB*, angiotensin II receptor blockers; *CCB*, calcium channel blockers; *ERAs*, endothelin receptor antagonists; *ANA*, antinuclear antibodies; *ACA*, anti-centromere antibodies; *Scl-70*, anti-Scl-70 antibodies; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein

NVC measurements and markers of macrovascular disease

The macro- and microvascular parameters under study in the total population are presented in Table 2. A Bland–Altman plot (Supplementary Fig. 1) showed acceptable agreement between the two investigators for the results of the NVC, with the mean difference being not statistically significant for all the NVC parameters. Moreover, a strong agreement was evidenced between the two investigators regarding the NVC patterns (kappa statistics: 0.981; $p < 0.001$).

Table 3 depicts the pairwise comparisons for the macrovascular parameters and the trends among the three NVC patterns (early, active, and late). Alx-75 was significantly lower in the early compared to late pattern (30.81 ± 11.59 vs 35.21 ± 7.90, $p = 0.003$) while higher Alx-75 values were observed across NVC patterns indicating more severe disease ($p = 0.027$). No significant correlations were found for cIMT and PWV. The results of the bivariate correlations between macro- and microvascular parameters are presented in Table 4. Again, AIx-75 was significantly correlated with

Table 2 Macro- and microvascular parameters in the study population

Parameter	Values
N	81
IMT right (mm)	0.61 ± 0.12
IMT left (mm)	0.62 ± 0.14
IMT mean (mm)	0.62 ± 0.11
HR (n/sec)	74.56 ± 9.49
SBP (mmHg)	128.53 ± 20.25
DBP (mmHg)	76.53 ± 10.14
PP (mmHg)	52 ± 16.73
CSBP (mmHg)	119.96 ± 20
CDBP (mmHg)	78 ± 10.29
CPP (mmHg)	41.96 ± 15.67
AIx (%)	30.96 ± 11.57
AIx75 (%)	30.47 ± 10.99
AP (mmHg)	13.79 ± 7.84
PWV (m/sec)	8.13 ± 2.46
capillaries (n/mm)	6 [3]
Avascular areas (n/mm)	2 [3.5]
Edema (n/mm)	1 [2]
Microhemorrhages (n/mm)	0 [0]
Enlarged loops (loops/mm)	2 [2]
Giant capillaries (loops/mm)	1 [1]
Ramified capillaries (loops/mm)	1 [1]
Bushy capillaries (loops/mm)	0 [0]
Tortuous capillaries (loops/mm)	0 [1]

Abbreviations: *IMT*, intima-media thickness; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *PP*, pulse pressure; *CSBP*, central systolic blood pressure; *CDBP*, central diastolic blood pressure; *CPP*, central pulse pressure; *AIx*, augmentation index; *AIx(75)*, heart rate-corrected augmentation index; *AP*, augmentation pressure; *PWV*, pulse wave velocity

capillary density expressed by the number of capillaries and ramifications (r = −0.262, $p = 0.018$, and r = 0.420, $p = 0.004$ respectively) (Fig. 1A). With regard to the association between PWV and the capillaroscopic parameters, a significant correlation was noted only with the number of enlarged loops (p = 0.024). Otherwise, no associations between other indices of morphological (cIMT) or functional parameters (PWV) of atherosclerosis were noticed.

AIx-75 was significantly associated with age (r = 0.283, p = 0.010). In addition to this, a borderline association between Alx-75 and antihypertensive treatment with angiotensin II receptor blockers (ARBs) was observed (r = 0.215, p = 0.054). However, adjustment for confounding variables, including age and antihypertensive treatment with ARBs, performed through a multivariate regression analysis was not found to affect the correlation between Alx-75 and capillary density, demonstrating an independent association between Alx-75 and the number of capillary ramifications (beta = 0.281, t = 2.33, p = 0.006).

NVC measurements and central and peripheral hemodynamics

In between-group comparisons, SSc patients with early and active NVC pattern had significantly lower augmentation pressure (AP) compared to late pattern (12.76 ± 6.51 vs 18.19 ± 9.74, p = 0.019, and 12.76 ± 6.51 vs 18.19 ± 9.74, p = 0.016 respectively), whereas central pulse pressure (CPP) was marginally lower (p = 0.067) (Table 3). In total, a significant trend was noted for CPP and AP amongst capillaroscopic patterns indicating progressive microvasculopathy (p = 0.046 and p = 0.017, respectively).

Correlation analysis between capillaroscopic abnormalities and hemodynamics revealed negative correlation between reduced capillaries and AP (r = −0.249, p = 0.025). DBP and cDBP were associated with microbleeding areas (r = 0.028, p = 0.041; r = 0.223, p = 0.046; respectively). The number of ramified capillaries were observed to have a significant positive correlation with cSBP (r = 0.223, p = 0.045). All statistically significant correlations were to the same direction after multiple comparisons correction (Table 4). Nevertheless, after inserting cSBP in a multivariate model along with Aix-75, age, hypertension, and antihypertensive treatment, Aix-75 was once again the only parameter found to be independently associated with capillary ramifications (beta = 0.322, t = 2.534, p = 0.004).

NVC measurements and CV score algorithms

CV risk estimations by Framingham Risk Score and ASCVD were progressively increasing in SSc patients with an early, active, or late NVC pattern of microangiopathy (p = 0.023, p = 0.019 respectively) (Fig. 2). Patients presenting active pattern in NVC had significantly lower scores compared to those with late pattern in all risk algorithms evaluated (Framingham Risk Score 2.99 ± 2.72 vs 6.36 ± 5.65 p = 0.027, QRISK3 7.80 ± 6.62 vs 12.57 ± 8.29 p = 0.029, ASCVD Risk 5.63 ± 4.41 vs 12.09 ± 9.90 p = 0.030) (Table 3). QRISK3 and ASCVD were numerically lower in the early compared with the late pattern (8.33 ± 5.87 vs 12.57 ± 8.29 p = 0.063, 6.99 ± 7.18 vs 12.09 ± 9.90 p = 0.082, respectively). As shown in Table 4, QRISK3 and ASCVD were negatively correlated with the number of capillaries (r = −0.231, p = 0.048; r = −0.260, p = 0.038); i.e., the lower the capillary density, the higher the risk of cardiovascular events. Moreover, QRISK3 was significantly correlated with the number of avascular areas/mm (r = 0.291, p = 0.012), indicating a strong association between desertification in NVC and higher cardiovascular risk.

Table 3 Macrovasculopathy markers in the NVC patterns

Parameter	EARLY	ACTIVE	LATE	p early vs active	p active vs late	p early vs late	p total
N	25	37	19				
cIMT mean (mm)	0.64 ± 0.11	0.59 ± 0.11	0.63 ± 0.13	0.064	0.333	0.569	0.194
CSBP (mmHg)	119.52 ± 20.42	117.51 ± 14.04	125.32 ± 28.02	0.648	0.265	0.432	0.386
CDBP (mmHg)	79.40 ± 9.63	78.27 ± 10.16	75.63 ± 11.48	0.527	0.382	0.204	0.359
CPP (mmHg)	40.12 ± 14.43	39.24 ± 10.75	49.68 ± 22.37	0.785	0.067	0.115	**0.046**
AIX (%)	28.24 ± 11.75	30.41 ± 11.57	35.63 ± 10.47	0.475	0.057	**0.036**	0.080
AIx75 (%)	26.36 ± 10.90	30.81 ± 11.59	35.21 ± 7.90	0.134	0.101	**0.003**	**0.027**
AP (mmHg)	11.98 ± 7.08	12.76 ± 6.51	18.19 ± 9.74	0.570	**0.016**	**0.019**	**0.017**
PWV (m/sec)	8.30 ± 2.02	7.71 ± 2.26	8.75 ± 3.23	0.143	0.166	0.574	0.270
N	23	32	18				
Framingham Risk Score	4.10 ± 4.13	2.99 ± 2.72	6.36 ± 5.65	0.236	**0.027**	0.147	**0.023**
N	23	33	18				
QRISK3	8.33 ± 5.87	7.80 ± 6.62	12.57 ± 8.29	0.543	**0.029**	0.063	0.054
N	22	28	14				
ASCVD Risk	6.99 ± 7.18	5.63 ± 4.41	12.09 ± 9.90	0.413	**0.030**	0.082	**0.019**

Abbreviations: *cIMT*, carotid intima-media thickness; *CSBP*, central systolic blood pressure; *CDBP*, central diastolic blood pressure; *CPP*, central pulse pressure; *AIx*, augmentation index; *AIx(75)*, heart rate-corrected augmentation index; *AP*, augmentation pressure; *PWV*, pulse wave velocity; *QRISK3*, 10-year cardiovascular disease risk; *ASCVD*, risk for heart disease and stroke using the 2013 ACC/AHA guidelines

Discussion

This cross-sectional single-center study examined the potential association between NVC measurements and indices of arteriosclerosis, central/peripheral hemodynamics, and CV risk algorithms in SSc patients. Our findings demonstrate that morphological markers of microcirculatory dysregulation, namely reduced capillary density and increased capillary dimensions (e.g., ramifications), are positively correlated with increased Alx-75 suggesting a relationship between large vessel dysfunction and capillary rarefaction. In addition, worsening phases of SSc-related microangiopathy characterized by late NVC pattern were related with higher values of central pulse pressure, arterial stiffness, and CV risk scores. Overall, the results of the study reveal a linear association between progressing peripheral microvascular damage and increased CV disease risk associated with accelerated atherosclerosis in individuals suffering from SSc.

The role of macrovascular and microvascular involvement in the development of CV disease remains a challenge in SSc, as endothelial dysfunction represents not only an atherosclerotic process but also the main event in the pathogenesis of the disease itself, leading to systemic impairment of microcirculation including coronary small vessels [36, 37]. For example, avascular areas in the nailfold capillaries have been correlated with coronary microvascular dysfunction assessed by coronary flow reserve suggesting that microvessel damage in different anatomical areas might be driven by similar mechanisms of vascular injury [38]. With regard to large vessels, a number of studies have established notable associations between various indices of macrovascular disease and NVC changes observed in different stages of SSc microangiopathy. In particular, structural changes of palmar digital arteries assessed by color Doppler ultrasonography [39], abnormal peripheral blood perfusion in laser speckle contrast analysis [40], blunted response to flow-mediated dilatation of brachial arteries [18], and increased systemic arterial stiffness [20] have been found to correlate with the progression across capillaroscopy patterns from "early" to "late" according to their severity.

The present study concurs with previous observations and further expands their findings by demonstrating significant relationships between advanced microcirculatory changes and several aspects of macrovascular atherosclerotic disease such as arterial stiffening, CV risk scores, and central hemodynamics. Our findings support the hypothesis that micro- and macrovascular dysfunction in SSc are potentially interrelated and indicate the presence of generalized vascular dysregulation which in turn may contribute to the increased risk for CV disease among SSc patients.

Previous studies have reported that Alx-75, a marker of arterial stiffening and a predictor of CV disease morbidity, is impaired in patients with SSc [41, 42]. Alx-75 derives from the ascending aortic pressure waveform which is closely related to functional and structural changes of small arteries [43]. Subsequently, reduced pulsatility and blood flow coupled with increased vasoconstrictor tone and rarefaction of the small digital arteries in the late stages of SSc microangiopathy could be associated with abnormal aortic

Table 4 Correlations between markers of macrovascular disease and capillaroscopic findings. * indicates the correlations that were statistically significant after multiple testing correction with the Benjamini & Hochberg method (false discovery rate of 50%)

Parameters		Capillaries (n/mm)	Avascular areas (n/mm)	Edema (n/mm)	Microbleeding per mm2	Enlarged loops (loops/mm)	Giant capillaries (loops/mm)	Ramified capillaries (loops/mm)	Bushy capillaries (loops/mm)	Tortuous capillaries (loops/mm)	CSURI
cIMT mean (mm)	R	0.060	0.009	0.038	-0.098	-0.120	-0.149	0.059	-0.188	-0.105	-0.108
	P	0.596	0.938	0.739	0.384	0.288	0.185	0.600	0.093	0.353	0.338
SBP (mmHg)	R	-0.085	-0.008	0.105	0.108	0.077	-0.096	0.216	-0.135	0.061	0.006
	P	0.452	0.946	0.351	0.337	0.495	0.392	0.052	0.228	0.587	0.958
DBP (mmHg)	R	0.187	-0.175	-0.089	0.228	0.118	0.049	0.054	-0.145	-0.166	0.099
	P	0.095	0.118	0.430	**0.041***	0.295	0.667	0.631	0.195	0.140	0.377
CSBP (mmHg)	R	-0.052	-0.063	0.077	0.115	0.064	-0.088	0.223	-0.146	0.004	0.003
	P	0.643	0.574	0.496	0.307	0.572	0.434	**0.045***	0.194	0.974	0.977
CDBP (mmHg)	R	0.173	-0.144	-0.105	0.223	0.090	0.059	0.083	-0.115	-0.143	0.106
	P	0.122	0.200	0.349	**0.046***	0.424	0.602	0.462	0.306	0.203	0.346
CPP (mmHg)	R	-0.174	0.028	0.176	-0.046	0.012	-0.130	0.197	-0.129	0.028	-0.052
	P	0.121	0.802	0.116	0.684	0.914	0.247	0.078	0.252	0.806	0.645
AIx (%)	R	-0.218	0.151	0.096	0.092	-0.036	-0.141	0.156	0.071	0.022	-0.051
	P	0.050*	0.179	0.393	0.413	0.752	0.209	0.164	0.526	0.848	0.652
AIx(75) (%)	R	-0.262	0.180	0.147	0.132	-0.022	-0.069	0.320	0.084	0.031	-0.011
	P	**0.018***	0.107	0.189	0.241	0.844	0.542	**0.004***	0.458	0.786	0.925
AP (mmHg)	R	-0.249	0.133	0.133	0.049	-0.002	-0.185	0.218	-0.044	0.010	-0.105
	P	**0.025***	0.236	0.236	0.667	0.984	0.099	0.051	0.693	0.928	0.350
PWV (m/sec)	R	-0.050	0.048	-0.046	0.104	-0.251	-0.145	0.037	-0.057	0.067	-0.103
	P	0.655	0.670	0.680	0.356	**0.024***	0.198	0.741	0.611	0.553	0.360
Framingham Risk Score	R	-0.176	0.111	0.070	-0.176	-0.036	-0.241	0.016	-0.148	-0.001	-0.170
	P	0.136	0.351	0.557	0.137	0.765	**0.040***	0.894	0.210	0.994	0.151
QRISK3	R	-0.231	0.291	0.045	-0.169	-0.089	-0.184	0.167	-0.148	0.063	-0.151
	P	**0.048***	**0.012**	0.706	0.151	0.453	0.116	0.156	0.210	0.592	0.198
ASCVD	R	-0.260	0.174	0.138	-0.089	-0.100	-0.265	0.111	-0.182	0.048	-0.187
	P	**0.038***	0.170	0.277	0.482	0.432	**0.035***	0.383	0.151	0.707	0.139

Abbreviations: *cIMT*, carotid intima-media thickness; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *PP*, pulse pressure; *CSBP*, central systolic blood pressure; *CDBP*, central diastolic blood pressure; *CPP*, central pulse pressure; *AIx*, augmentation index; *AIx(75)*, heart rate-corrected augmentation index; *AP*, augmentation pressure; *PWV*, pulse wave velocity; *QRISK3*, 10-year cardiovascular disease risk; *ASCVD*, risk for heart disease and stroke using the 2013 ACC/AHA guidelines; *CSURI*, skin ulcer risk index

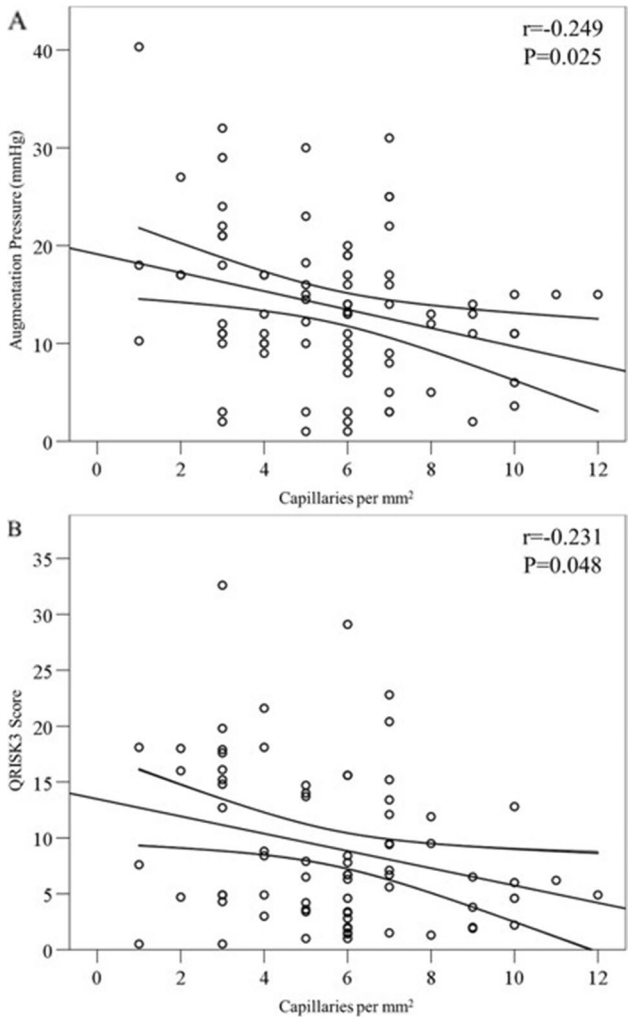

Fig. 1 Negative correlation between **A** augmentation pressure and **B** QRISK3 with capillary density, as assessed by NVC

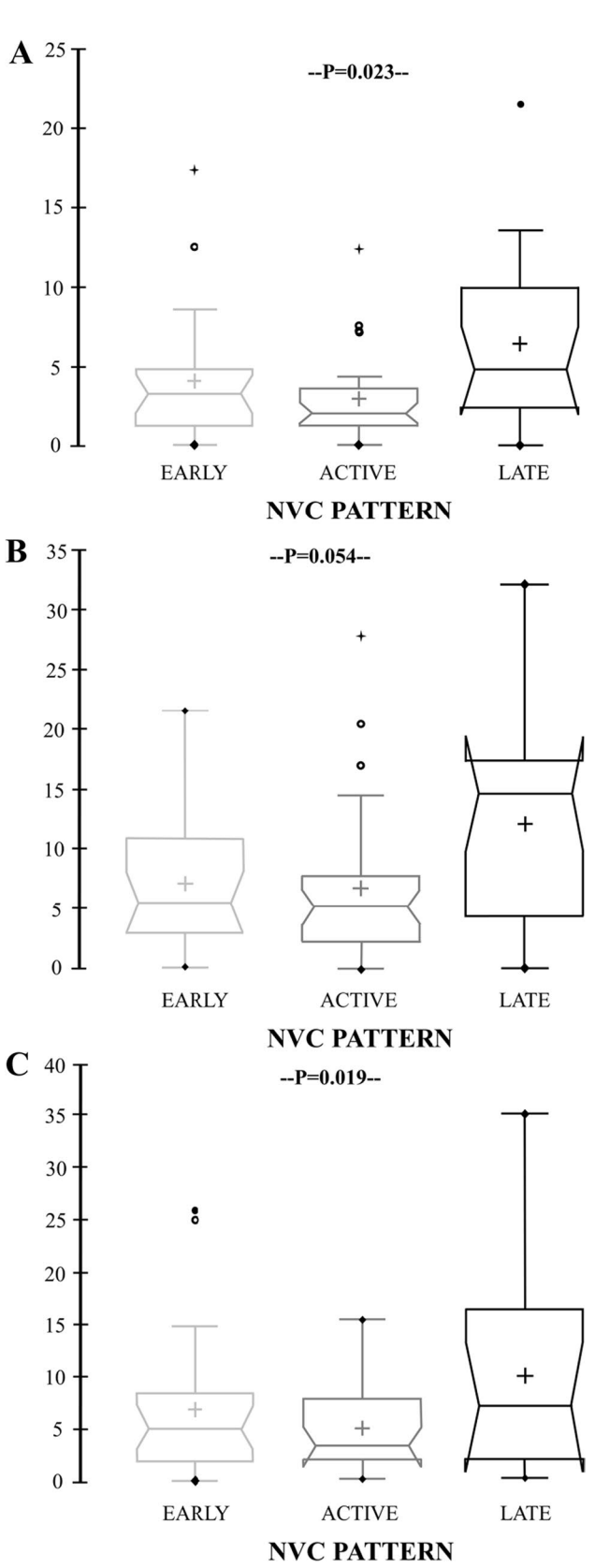

Fig. 2 Cardiovascular risk scores (**A**, Framingham Risk Score; **B**, QRISK3; **C**, ASCVD) in patients with different NVC patterns

elastic properties and peripheral artery resistance reflected in higher Alx-75 values. On the other hand, stiffening of the aorta increases pressure and flow pulsatility which may transmit distally and further enhance microcirculation damage in peripheral vascular trees [44]. To lend more support to this complex interrelation, a recent study found significant associations between aortic root dilatation assessed by echocardiography and severity of microvasculopathy in SSc patients [21]. Taken all together, it seems that functional and morphological alterations of large vessels are correlated with the diminution of capillary density and the extent of peripheral microvascular injury in SSc.

The relationship between CV disease and microvascular rarefaction associated with anomalies of capillary morphology appears to widen beyond the spectrum SSc and rheumatic diseases. An increasing number of studies over the recent years have demonstrated significant correlation between NVC changes and arterial stiffness, hypertension,

disease severity, and CV disease in different disease settings, namely chronic renal failure [45], renal cancer [46], pulmonary arterial hypertension [47, 48], diabetes mellitus respectively [49], as well as patients with paraneoplastic Raynaud's phenomenon [50]. As a result, NVC emerges as a novel tool for the assessment of peripheral microcirculation in several conditions but the validation of the findings in other diseases requires extensive research with pre-defined end points.

The performance of CV risk calculators developed for the general population in predicting future CV events in patients with systemic rheumatic diseases is poor as they appear to underestimate the risk, especially in rheumatoid arthritis [51]. In the context of SSc, only Ozen et al. investigated whether subclinical atherosclerosis could be detected with SCORE (Systematic Coronary Risk Evaluation) and QRISK I in a small number of SSc patients (n = 19) and yielded negative results [52]. In the current study, we found significant correlations between the degree of progression of microvasculopathy with increased scores of a broad spectrum of CV risk algorithms such as Framingham Risk Score, QRISK3, and ASCVD. This novel finding may provide further insight into the association between CV risk and peripheral microcirculatory changes and CV disease. Although these observations have to be confirmed in larger studies, the already reported association between progressive NVC patterns and internal organ involvement may suggest that the degree of microvasculopathy may also indicate patients at higher risk for CV events.

The main limitation of our study is the cross-sectional design which precludes temporal relationships and causal associations to be observed. Previous studies reported that antihypertensive drugs may mitigate Alx-75 abnormalities but treatment with such regimens did not appear to affect the results of the analysis. We also acknowledge that the associations established—particularly between Alx-75 and NVC patterns—are not robust enough to draw definite conclusions. On the other hand, the findings of the study may provide the rational for population-based, longitudinal studies with hard CV disease endpoints to determine the link between CV risk and microangiopathy in SSc. However, this is the largest study to date investigating the relationship between NVC alterations and subclinical atherosclerosis in SSc. Sample sizes of the NVC pattern groups may be considered relatively small, but the inflated type 2 error rate in the corresponding comparisons may be considered marginal, given that all relevant results were to the same direction. In addition, NVC was conducted in all fingers except thumbs and the acquisition of two adjacent images from each finger including qualitative and semi-quantitative assessment performed based on a validated algorithm proposed by Smith et al. [53]. Finally, we utilized an extensive panel of macro- and microvasculature assessments in a real-life population representative of average SSc patients attending scleroderma clinics.

In conclusion, our study points towards an association between CV risk and macrovascular atherosclerotic disease with worsening stages of peripheral microcirculation in patients with SSc. Whether NVC measurements could modify CV risk assessment in SSc patients should be determined in future studies.

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