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Original article

Detection of severe digital vasculopathy in systemic sclerosis by colour Doppler sonography is associated with digital ulcers

Susanne Lüders[1,*], Stefanie Friedrich[1,*], Sarah Ohrndorf[1] Anne-Marie Glimm[1], Gerd-Rüdiger Burmester[1], Gabriela Riemekasten[2,†] and Marina Backhaus[3,†]

Abstract

Objective. Colour Doppler ultrasonography (CDUS) is very important in general vascular diagnostic procedures. Its role in determining the extent of vasculopathy in Systemic Sclerosis (SSc) needs further investigation. The aim of this study was to compare the presence of altered arteries with nailfold capillaroscopy and clinical signs of ischaemia, that is, digital ulcers or pitting scars (DU/PS). A feasible CDUS protocol is provided.

Methods. Two thousand five hundred and twenty-eight arteries of the fingers, palms and wrists from 79 SSc patients (32 arteries per patient) were examined using CDUS. Furthermore, nailfold capillaroscopy, clinical and laboratory data were evaluated.

Results. Narrowed or occluded lumens were seen in 39.8% of all assessable arteries (n = 2489) and 48.9% of all proper palmar digital arteries (n = 1564) but only 15.6% ($P < 0.0001$) of proximal arteries (n = 924). Fingerwise analyses presented significant coincidence of pathological CDUS findings and DU/PS ($P = 0.0009$). Pathological CDUS findings were also associated with elevated CRP concentrations, current or past smoking with $\geqslant$20 pack-years, male gender and present or past DU/PS. Receiver operating characteristic curve analysis (area under the curve = 0.727) suggested a cut-off value of $\geqslant$20% pathological vessels (sensitivity: 90.7%; specificity: 47.8%) for the presence of DU/PS. An examination protocol focusing on the right-hand digits II–V (proper palmar digital arteries) revealed similar results (area under the curve = 0.751; sensitivity: 93.0%; specificity: 43.5%).

Conclusion. CDUS of hand and finger arteries allows measurement of the extent of SSc vasculopathy, which is associated with clinical signs of chronic malperfusion. A shortened examination protocol of CDUS (right-hand digits II–V; 15 min instead of 45 min examination time) could complement vascular diagnostics in SSc.

Key words: systemic sclerosis, colour Doppler ultrasonography, digital arteries, vasculopathy, malperfusion, digital ulcers, nailfold capillaroscopy

Rheumatology key messages

- In SSc, the extent of digital vasculopathy can be assessed well using colour Doppler ultrasonography.
- Ultrasonography results are associated with severe vascular complications, e.g. digital ulcers in SSc.

[1]Department of Rheumatology and Clinical Immunology, Charité University Hospital, Berlin, [2]Department of Rheumatology, University of Schleswig-Holstein, Lübeck and [3]Department of Internal Medicine – Rheumatology and Clinical Immunology, Park-Klinik Weissensee, Berlin, Germany

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*Susanne Lüders and Stefanie Friedrich contributed equally to this study

†Gabriela Riemekasten and Marina Backhaus contributed equally to this study

Correspondence to: Marina Backhaus, Department of Internal Medicine – Rheumatology and Clinical Immunology, Park-Klinik Weissensee Berlin, Academic Hospital of the Charité, Schoenstrasse 80, 13086 Berlin, Germany.
E-mail: marina.backhaus@charite.de

CLINICAL SCIENCE

Introduction

SSc is a rare but severe rheumatic disease associated with inflammation, vasculopathy and fibrosis. The vascular malfunctioning includes RP with inordinate vasospasm, disturbed microcirculation and a fibroproliferative occlusive vasculopathy of the distal arterial tree [1]. The contribution of these processes to clinical manifestations may determine the outcome and response to treatment. During disease progression, >50% of the patients develop complications attributable to acral ischaemia, such as pitting scars (PS) and digital ulcers (DU) [2]. These generally include pain, loss of function, reduced quality of life, work disability, need for help and increased risk for infection and amputation [3, 4].

Various efforts have been made in order to detect patients at risk for the development of DU and to define specific risk factors (e.g. smoking, male gender, antibody profile) [5–9]. Emphasis has also been placed on the detection of microvasculopathy via the examination of acral capillaries using nailfold capillaroscopy (NC) [5, 10–13]. Recently, the videoCAPillaroscopy (CAP) multicentre study defined the mean number of capillaries per millimetre in digit III of the dominant hand, the number of DU and signs of severe digital ischaemia at baseline as risk factors for the development of new DU during a 6-month follow-up [14]. There is also evidence that obstructive occlusions of the proper palmar digital arteries (PPDAs) are essential for the nutritive flow in the fingertip and might be associated with the development of DU [15, 16].

Colour Doppler ultrasonography (CDUS) is able to detect structural pathologies in the digital arteries, which do not appear in healthy subjects or patients with primary RP [17, 18]. Those changes, described as narrowing and occlusion of the arteries, where shown to be linked to the capillaroscopic pattern. However, Rosato *et al.* [19] did not find an association between structural pathologies of the arteries and the presence of DU. This might be because of a relatively low number of participants in the study as well as the lack of an investigation into the relationship of local macrovasculopathy (i.e. occluded digital arteries) and ischaemic complications in the same finger. Lescoat *et al.* [20] investigated the importance of the ulnar artery and the finger pulp blood flow for the development of DU in a prospective study of 55 SSc patients and 19 healthy controls using power Doppler ultrasonography. Pathological finger pulp blood flow as well as ulnar artery occlusions were found to be independent risk factors for the occurrence of new DU in a 1-year follow-up [20]. Frerix *et al.* [21] found differences in colour duplex sonography of the ulnar and radial arteries between SSc patients and controls. They also showed that the development of DU during follow-up was linked to ulnar artery occlusions.

The present study represents the first attempt to investigate arterial alterations in each finger individually and the concordance of arterial alterations and present signs of ischaemia. Therefore, CDUS, NC as well as clinical and laboratory findings of SSc patients were compared on a relatively large scale. Furthermore, the present work constitutes a thorough investigation into the detection of cut-offs as well as marker fingers for current DU or PS (in a similar manner to the use of the US7-Score of the most affected joints to evaluate the disease severity in RA [22, 23]). These could optimize the CDUS examination for the detection of arterial alterations and promote risk stratification for future vasculopathy-related complications in a relatively short examination time.

Methods

Ethical approval was granted by the local ethical committee (Ethikkommission der Charité – Universitätsmedizin Berlin, EA1/269/13). We collected written consent forms from all subjects before the examinations.

Subjects' characteristics

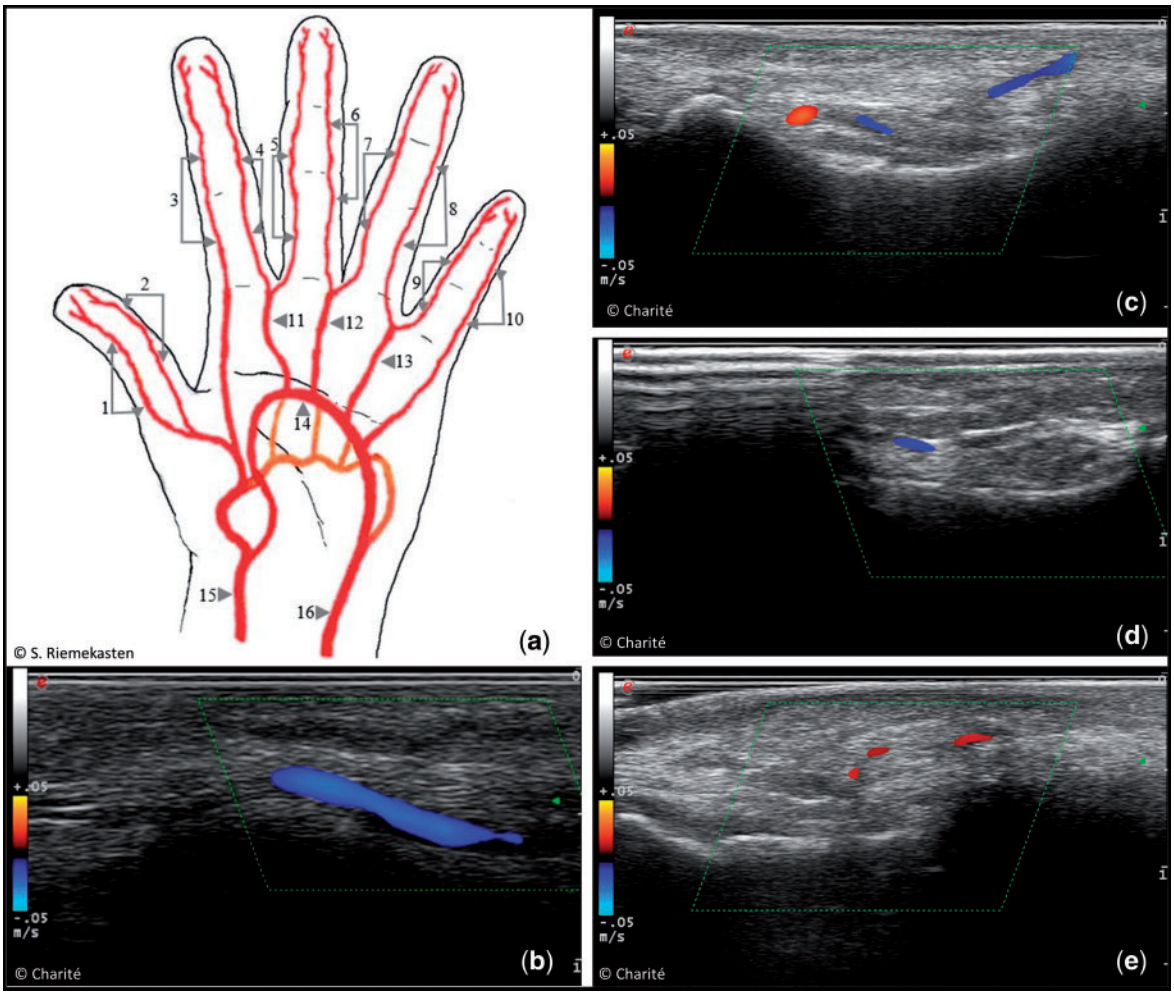
Seventy-nine patients fulfilling the 2013 ACR criteria for SSc were included [50 limited and 29 dcSSc, 82.3% female, mean (S.D.) age 56.47 (14.3) years; mean (S.D.) duration since first Raynaud's episode 13.1 (12.7) years, mean (S.D.) disease duration 9.4 (8.7) years]. We detected primary ischaemic and ischaemia-related DU and PS. We consecutively included inpatients of the rheumatology ward as well as outpatients of the rheumatology daily care unit. There was no selection for or restriction of any ongoing treatment. Current treatments included i.v. iloprost (55.7% of patients), calcium channel blockers (44.3%), angiotensin-converting enzyme inhibitors (20.2%), Angiotensin-II-receptor-1-antagonists (15.2%), endothelin receptor antagonists (15.2%), Phosphodiesterase type 5 inhibitors (10.1%) and α-blockers (2.5%). Of the patients treated with i.v. iloprost, 65.9% were also receiving oral vasodilators. Of the patients without current iloprost treatment, 67.6% received oral vasodilators.

CDUS

Examination was done in a room with an ambient temperature of 21 °C using a linear array transducer (9.1 MHz) of the ultrasonographic device Mylab Twice (Esaote, Genua, Italy). Sonography of the arteries of the wrists, palms and fingers was performed according to Schmidt *et al*. [17, 18]. After a 5 min water bath at ~38 °C, 16 arteries of each hand were examined, with the palms facing upward (Fig. 1A). The second hand to be examined was kept warm until its turn. The entire examination time—including preparation, ultrasonography and arterial grading—lasted 45 min on average. CDUS was performed by two sonographers trained in the sonographic evaluation of the arteries of the fingers and hands.

Depending on the morphological appearance and colour Doppler signal, we graded the arteries as wide, narrowed or occluded. Wide vessels with homogeneous colour signals and pulsation were considered normal (see Fig. 1B), whereas narrowed or occluded arteries constituted pathological findings. As vessel calibres

FIG. 1 Colour Doppler ultrasonography of the arteries of fingers, palms and wrists



(**A**) The arteries examined are as follows: 1–10: proper palmar digital arteries (PPDAs); 11–13: common palmar digital arteries (CPDAs); 14: superficial palmar arch (SPA); 15: radial artery (RA); and 16: ulnar artery (UA). The probe was placed at every point marked by an arrowhead. (**B**) Screenshot of a normal PPDA with a broad and homogeneous colour signal. On the right-hand side are pathological vessels with narrowed arteries (**C**), occluded arteries (**D**) and collateral flow (**E**).

show individual variation, narrowed vessels were defined by their morphological appearance rather than diameter. They showed a reduced Doppler signal (see Fig. 1C) and pulsation as well as greater difficulty in delineating their course because they were frequently twisted. If an artery was not seen in B-mode or pulse wave Doppler, it was considered occluded (compare Fig. 1D).

NC

This method was conducted with a USB device (Di-Li 970-O USB hand-microscope Di-Li-Lite) and MicroCapture V2.0 software (to determine the capillary density) following current guidelines. We assessed morphological changes and the minimal density of capillaries in the nailfold of digits II–V of both hands. According to Cutolo *et al.*, [24] we assigned a capillaroscopic pattern to each patient as early, active or late, which present different combinations of SSc-specific alterations. Normal or other pathological NC findings were summarized as non-SSc specific [10, 24, 25].

NC and CDUS were performed by two trained examiners (S.L., S.F.). As a general rule, the same examiner could not perform both the CDUS and the NC in one individual. Both examinations took place on the same or on two consecutive days.

Statistical analysis

Univariate (Mann–Whitney *U*-test, χ^2 and Fischer's exact test) and receiver operating characteristic (ROC) curve analyses were conducted where appropriate using SPSS (software version 21.0.0.2) and GraphPad Prism (software version 5.00). A value of $P \leqslant 0.05$ was considered statistically significant.

Results

CDUS shows a high presence of angiopathy in the digital arteries of SSc patients

Two thousand five hundred and twenty-eight arteries were analysed in total. Thirty-nine arteries (1.5%) could not be assessed because of severe sclerodactyly, active ulcers or the position of an i.v. catheter. Of the assessable arteries, 39.8% were pathological, meaning narrowed or occluded.

The PPDAs were significantly more often affected by morphological changes (48.9% pathological) than the proximal vessels of the palms and wrists (15.6% pathological; $P < 0.0001$). Figure 2 depicts the percentage of pathological findings per artery and hand for the entire cohort; for example, the radial PPDA of the index fingers was either narrowed or occluded in >75% of the patients. Comparing the arteries of the wrists, a higher percentage of pathologies could be found for both ulnar arteries (narrowed or occluded: 21.8% in the left and 23.0% in the right ulnar artery vs 2.6% in the left and 5.4% in the right radial artery). There was no significant difference between the corresponding arteries of the right and left hand regarding the total proportion of pathological vessels. Differentiating between narrowed and occluded arteries, there was a slightly higher percentage of occluded vessels in the right-hand digits I–III (PPDA I radial to PPDA III ulnar arteries) compared with the left hand. The right-hand PPDA IV radial and ulnar arteries showed more narrowed arteries than their corresponding partners ($P = 0.07$).

Pathological arteries observed by CDUS are linked to clinical signs of ischaemia in the same finger

Figure 3 depicts the number of patients with current DU and/or PS per finger as well as the overall count of DU/PS in each finger for the SSc cohort. Both the number of patients with DU/PS and the quantity of DU/PS was highest in the index fingers of both hands. Both hands showed the same overall amount of ischaemia-related complications, with 131 DU/PS on the left and 132 DU/PS on the right hands.

In SSc patients, 161 fingers (20.4% of all 790 fingers) presented DU and PS at the time of examination. Of those fingers, 80.7% presented at least one pathological PPDA (34.2% occluded) in CDUS. Of the 629 fingers without skin lesions, a significantly smaller percentage (67.4%, $P = 0.0009$) showed morphological alterations in one or both PPDAs in CDUS (20.7% occluded; $P = 0.0005$).

ROC curve analysis supported these findings, in that fingers with vasculopathy in CDUS often presented clinical signs of malperfusion (area under the curve = 0.727 for all fingers). We calculated a 90.7% sensitivity and a 47.8% specificity with ⩾20% pathological vessels as the cut-off.

In univariate analysis, the odds ratio (OR) for a finger with at least one pathological (i.e. narrowed or occluded) PPDA in CDUS to present DU or PS was twice as high as for a finger with a set of two wide PPDAs (OR = 2.1; 95% CI: 1.3, 3.1). Fingers with at least one occluded PPDA were more prone to present DU/PS (OR = 2.0; 95% CI: 1.4, 2.9) than fingers with a set of two wide, a set of one wide and one narrowed or a set of two narrowed PPDAs. The general presence of DU and/or PS seemed to be more likely when vascular pathologies of the right-hand fingers occurred; ORs of the right-hand fingers ranged from 1.5 (95% CI: 0.5, 4.5) in the index finger to 6.8 (95% CI: 2.4, 19.4) in digit IV [compared with OR values from 1.2 (95% CI: 0.5, 2.9) to 3.4 (95% CI: 1.3, 8.6) in the left hand].

The percentage of pathological vessels for each patient is associated with disease severity

In our cohort, the percentages of pathological vessels per patient varied considerably, especially in limited SSc [mean 35.4% (95% CI: 28.0, 42.7%)]. Here, we found both extremes; two patients had exclusively normal (i.e. wide) arteries, whereas one subject presented exclusively pathological arteries (i.e. narrowed or occluded) in their hands. Patients with dcSSc showed arterial alterations in CDUS slightly more often [mean 38.8% of pathological vessels (95% CI: 33.4, 44.1%); $P = 0.0889$].

In univariate analysis, increased percentages of pathological arteries were associated with male gender, current and past smoking with ⩾20 pack-years, CRP concentrations >0.5 mg/dl, and subjects with past and current DU and/or PS (Fig. 4). Subjects who reported no restrictions attributable to RP in the last week showed fewer alterations in CDUS compared with those with RP present in the last week [mean 26.4% (95% CI: 14.6, 38.2%) *vs* 38.4% (95% CI: 32.8, 44.1%); $P = 0.0488$].

Patients with ongoing iloprost treatment had a higher percentage of pathological vessels [mean 46.2% (95% CI: 35.0, 49.4%) *vs* 29.6% (95% CI: 23.3, 36.0%) in patients without i.v. iloprost treatment; $P = 0.0316$].

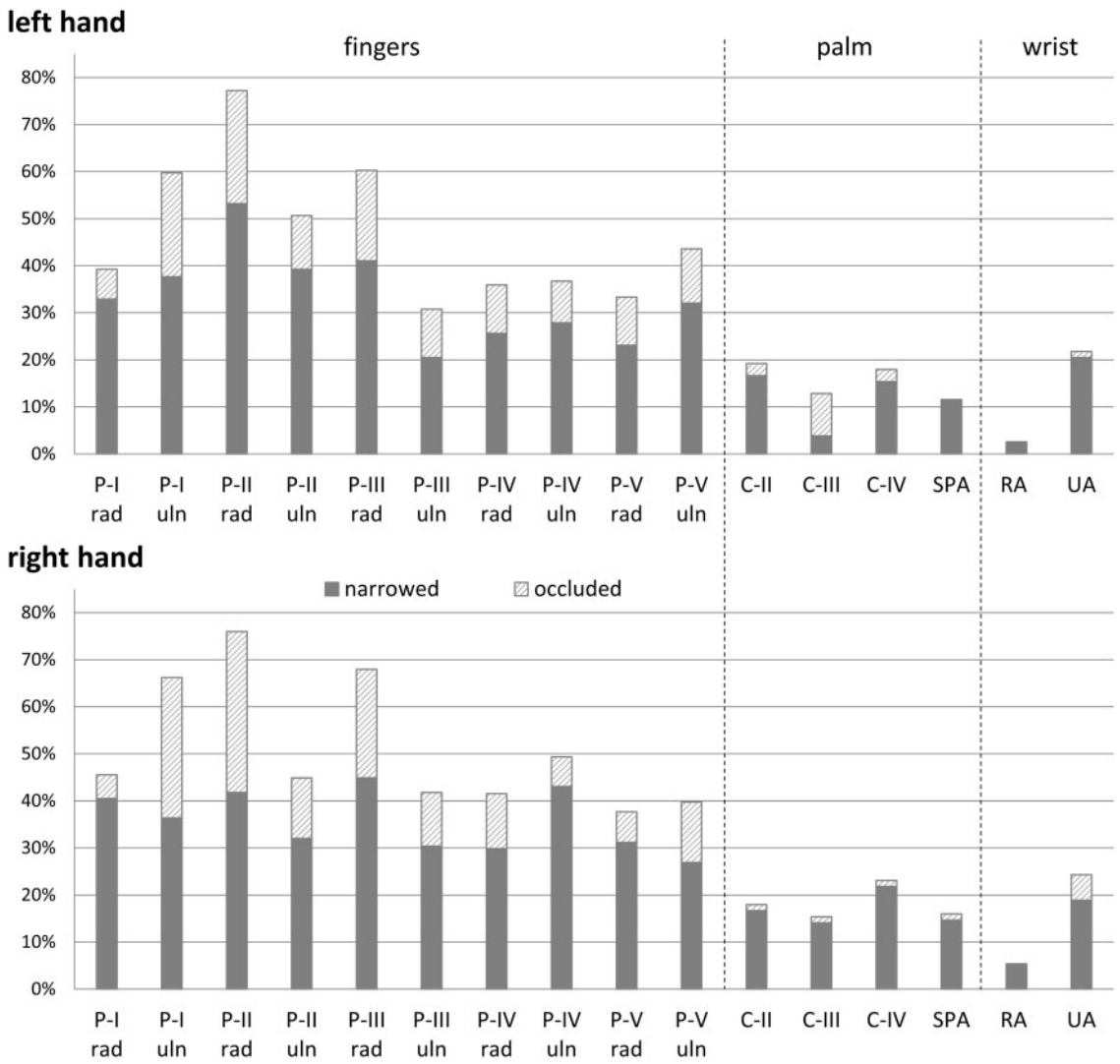
No associations were found between CDUS findings and age, disease duration or the modified Rodnan skin score (data not shown).

Patients with an advanced pattern on NC revealed a higher percentage of DU

Assuming a link between macrovasculopathy and microvasculopathy, we analysed 79 patients by NC. As 19 patients had no megacapillaries, we could not calculate the capillaroscopic skin ulcer risk index [11] and therefore chose to analyse capillaroscopic patterns as described by Cutolo *et al.* [24]. Two patients showed a non-SSc-specific pattern (2.5%), 13 presented an early (16.5%), 28 an active (35.4%) and 33 a late pattern (41.7%); 3 were not assessable. No patient with a non-SSc-specific pattern revealed current DU/PS. In contrast, 38.5% of patients with an early, 57.1% of patients with an active and 63.6% of patients with a late pattern displayed current DU/PS ($P = 0.2995$).

In addition, patients with a non-SSc-specific or early pattern in capillaroscopy tended to have a lower number of pathological arteries in CDUS than patients with an active or late pattern [mean 28.3% (non-SSc and early pattern combined, 95% CI: 16.6, 40.0%) vs 38.8% (active and late pattern combined, 95% CI: 33.0, 44.5%), respectively; $P = 0.0757$] There was no significant difference in the

FIG. 2 Percentage of pathological vessels (narrowed or occluded) per artery and hand in all 79 SSc patients



Percentage of pathological vessels (narrowed or occluded) per artery and hand (left hand: top; right hand: bottom) in all 79 SSc patients. C: common palmar digital artery; P: proper palmar digital artery; SPA: superficial palmar arch; RA: radial artery; UA: ulnar artery; rad: radial; uln: ulnar.

number of pathological vessels in patients with a late pattern compared with the other patterns (non-SSc, early and active pattern) put together [mean 38.2% (95% CI: 30.1, 46.2%) *vs* 35.5% (95% CI: 28.6, 42.5%); P = 0.5220].

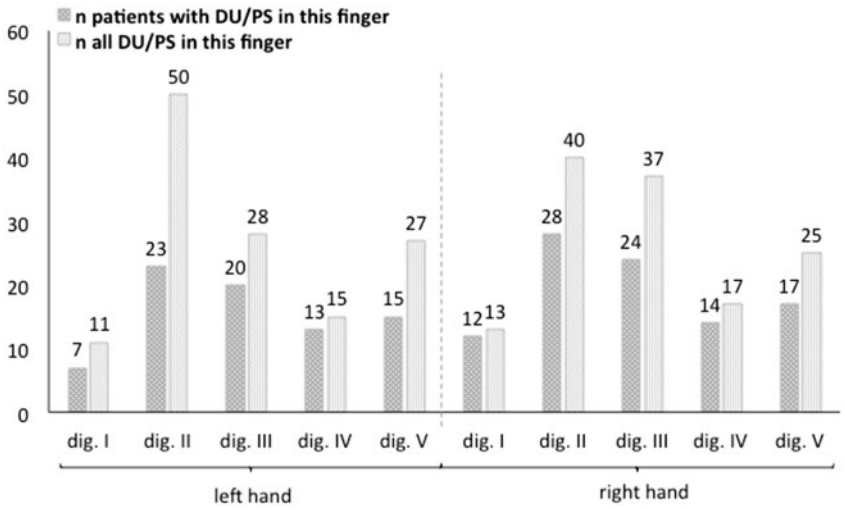
However, there was no link between reduced capillary density <7/mm in NC, which was present in 79% of assessable fingers, and the existence of pathological vessels in CDUS.

A simplified CDUS protocol is sufficient to estimate the extent of macrovasculopathy as well as its connection to DU/PS

Statistical analysis revealed a significant correlation between sonographic findings for the PPDAs of digits II–V of the right hand and the general presence of DU/PS. These eight arteries showed a mean of 59.5% pathological signs (95% CI: 50.5, 68.5%) in patients with DU/PS and a mean of 31.8% (95% CI: 23.5, 40.2%; P < 0.0001) in patients without DU/PS.

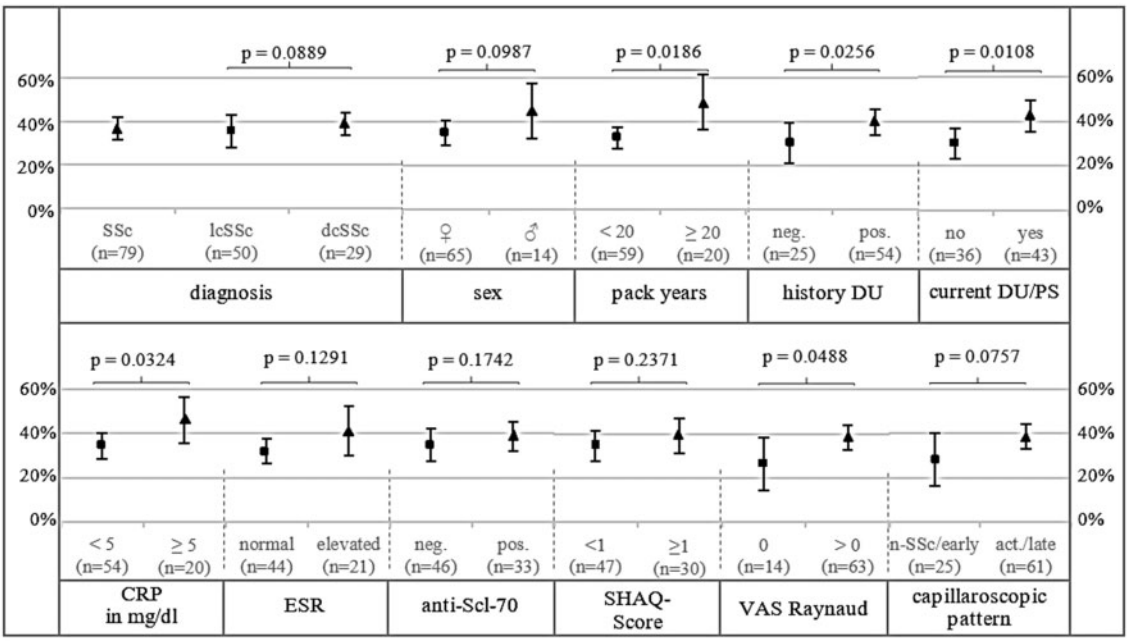
Compared with the ROC curve analysis of all 32 arteries of the fingers, palms and wrists (see above), a ROC curve analysis of the 8 PPDAs (digits II–V of the right hand) revealed a slightly improved concordance between pathological CDUS findings and the general presence of DU/PS (area under the curve = 0.751; see Fig. 5). For the previously determined cut-off (⩾20% pathological vessels), sensitivity increased to 93.0% and specificity amounted to 43.5%.

Fig. 3 Digital ulcers and pitting scars per finger



Number of SSc patients with DU and/or PS per finger and number of all DU/PS per finger in the SSc cohort. dig: digit; DU: digital ulcers; PS: pitting scars.

Fig. 4 Ultrasonography results depending on demographic and clinical characteristics



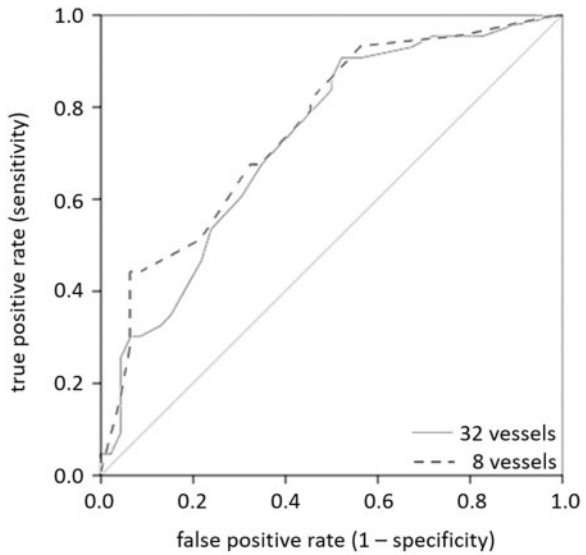
Mean and 95% CI of percentage of pathological vessels depending on demographic and clinical characteristics of SSc patients (n = 79). DU: digital ulcers; PS: pitting scars; SHAQ: scleroderma health assessment questionnaire; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; anti-Scl-70: Anti-Scl-70 antibody/antibody against topoisomerase I; lcSSc: limited (cutaneous) systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; neg.: negative; pos.: positive; n-SSc: non-SSc pattern; act.: active pattern.

Similar results were obtained for NC pattern recognition and current DU/PS: 88.1% sensitivity and 45.5% specificity, with the active and late patterns considered as the test positives.

Discussion

CDUS offers a complementary tool to assess structural vasculopathy in SSc. This may be important because

Fig. 5 Receiver operating characteristic curve analysis of ultrasonography for the extended and the shortened protocol



ROC curve analysis with sensitivity and specificity for current digital ulcers or pitting scars depending on the percentage of pathological vessels either of all 32 arteries examined (continuous line) or of the eight arteries of digit II–V of the right hand (dashed line). ROC: receiver operating characteristic.

major vascular complications in SSc, such as chronic and recurrent DU, occur in a subset of patients. As recently presented, this subset is likely to have a higher disease burden [26]. It is therefore crucial to identify patients with a high risk of vascular complications. As structural changes of the arteries are an important part of the pathophysiological model of the vascular disease in SSc, assessment of the digital arteries could help to identify this subset.

In agreement with previous studies, structural changes in the arteries at the level of the wrists and hands detected by CDUS are very common in SSc patients, and ulnar artery occlusions have already been identified as a risk factor for new DU [17–21]. The extent of these vascular alterations differs among patients and different arteries. Although narrowed lumens or occlusions were apparent in almost half of all digital arteries (PPDAs), they were rarely present in the more proximal vessels. As the corresponding arteries of both hands showed a similar extent of vasculopathy in CDUS, dexterity seems to be immaterial.

Although other longitudinal studies have shown a significant link between the late pattern in NC and the development of DU [10, 27, 28], we could not find a significant association between those factors at baseline in our cross-sectional design. In our study, DU and PS were predominantly found in the same fingers that presented the highest percentages of pathological—and especially occluded—arteries (compare Figs 2 and 3). These findings guided us to a specific fingerwise analysis, which revealed a significant co-occurrence of vasculopathy as seen in CDUS and concomitant DU/PS in the same finger.

In patients with SSc, current or past DU and PS significantly coincided with a considerable number of narrowed or occluded digital arteries. Known risk factors for the development of DU, such as male gender, smoking and anti-Scl-70 antibodies, were also linked to high proportions of pathological arteries in CDUS (see Fig. 4), supporting the role of this method and our analysis as a possible marker of DU/PS. These findings are partly in contrast to observations made by Rosato *et al.* [19], who did not find an association between CDUS and the history or presence of DU/PS. This may be the result of a reduced comparability because of differences in arterial grading and our additional fingerwise evaluation.

CDUS, albeit practical, is a time-consuming examination. During data collection, difficulties in the categorization of the thumbs' PPDA occurred. The findings of this study therefore suggest a reduced examination of digits II–V selectively, as seen in other diagnostics, such as NC. The sensitivity and specificity of sonographic findings for the general presence of skin lesions even improved when focusing on the PPDAs of digits II–V of the right hand. We obtained these results following a similar rationale to Smith *et al.* [13] in their 2011 manuscript on NC in day-to-day practice. Thus, CDUS of these eight digital arteries could be conducted in $<$15 min. This simplified and less time-consuming CDUS protocol is a feasible method that shows a significant association between vasculopathy of the hands and DU/PS at baseline, with similar sensitivity and specificity compared with NC patterns. The data of other studies also allow the calculation of high sensitivity and medium specificity levels for NC patterns concerning DU at baseline. Using the European Scleroderma Trials and Research group (EUSTAR) database including 2754 SSc patients, we calculated the specificity levels of the active and late pattern for the presence of DU at baseline and obtained 46% specificity (75% sensitivity) [12]. Caramashi *et al.* [29] performed capillaroscopy in 103 patients. Based on their data, we calculated 43% specificity and 88% sensitivity for the active/late pattern concerning the presence of DU. These are very similar results to those mentioned in our manuscript. Future studies should investigate the liaison between PPDA pathologies seen in CDUS and the mean capillary density in NC as proposed in the CAP multicentre study [14].

Although the present study focused on the association of CDUS and the presence of DU, some other clinical parameters as well as the results of capillaroscopy were also compared with sonographic findings (e.g. Fig. 4). These results are of an explorative nature and should be confirmed in future studies, especially as some of those results could not be considered significant if an adjusted P-value was applied (i.e. Bonferroni correction). However, the main results were not affected by an adjusted P-value.

Study limitations of this project also include different therapies and their possible effects on vascular

performance during CDUS. However, we tried to minimize the effects of vasoactive therapies by a warm water bath before CDUS in order to provide comparable conditions for each patient to distinguish structural from functional alterations. This and the adaptation of the treatment to the severity of the disease might be the reason for the apparent contradiction that patients with ongoing iloprost therapy had a higher number of pathological vessels. Nonetheless, the influence of vasoactive therapies on CDUS findings as well as their inter- and intrareader reliability should be evaluated further.

In addition, a possible limitation of sonography might be that long-lasting vascular changes may lead to natural bypasses owing to local ischaemia. Such circumventions could not be assessed properly via the CDUS protocol used in the present study (Fig. 1E), which means that observed vasculopathies may coexist with a sufficient tissue perfusion (as suggested by the presence of patients showing a high number of pathological vessels without any current DU/PS). Freire *et al.* [30] found power Doppler signals in the finger pads as signs of distal vascularization in all of their healthy subjects as well as in 59% of SSc patients. Lescoat *et al.* [20] found pathological finger pulp blood flow to be a risk factor for the development of future DU. Examination of the finger pulp could therefore be a valuable addition to our proposed CDUS protocol and should be investigated further.

In conclusion, CDUS is able to detect digital vasculopathy in patients with SSc. Following the simplified protocol, CDUS could be assessed as a prognostic tool for the development of DU in patients with SSc in future studies.

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