Original Article

Superb Micro Vascular Imaging as a Novel Tool for the Assessment of Blood Flow Velocity in Patients with Systemic Sclerosis: A Single-Center Feasibility Study

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Featured Application: Superb Micro Vascular Imaging (MVI) is a novel ultrasound-based imaging technique used for areas with low blood flow velocities. This is the first report of the feasibility of MVI in blood flow velocity assessment in Systemic Sclerosis patients.

Abstract: Systemic sclerosis is an autoimmune disease characterized by organ fibrosis and vasculopathy. Almost all patients suffer from Raynaud's phenomenon. Nailfold video capillaroscopy is the most widely available imaging technique, but flow quantification is impossible. Therefore, novel imaging techniques are of interest. We performed a single-center feasibility study using Micro Vascular Imaging (MVI) for flow quantification of small fingertip vessels. We compared 20 healthy controls (HCs) with 20 Systemic Sclerosis (SSc) patients. In HCs, measurements were, on average, statistically significantly higher combined for all fingers (median 10.68 vs. 6 cm/s, Δ=4.68 cm/s, $p<0.0001$) and for individual fingers. An optimal cut-off value of peak systolic (PS) velocity of <6.13 cm/s and end-diastolic (ED) velocity of <2.13 cm/s discriminated HCs from SSc. Test characteristics for PS showed excellent sensitivity (0.90, 95% CI 0.70-0.98) and specificity (0.85, 95% CI 0.64-0.95; LR+ 6.0). For ED velocity, sensitivity was 0.85 (95% CI 0.64-0.95), specificity was 0.80 (95% CI 0.58-0.92, LR+ 4.25). Here, we present the first study on the use of MVI to assess blood flow in the fingertips with high sensitivity and specificity in SSc. Future studies need to investigate correlations with the risk of organ complications, such as digital ulcers or pulmonary arterial hypertension.

Keywords: Systemic Sclerosis, Raynaud's phenomenon, ultrasound, microvascular imaging, blood flow.

1. Introduction

Systemic Sclerosis (SSc) is a systemic autoimmune disorder characterized by skin and organ fibrosis and vasculopathy [1]. The latter affects about 90-100% of patients; clinically, this is evident by the presence of Raynaud's phenomenon (RP) and potential complications, including digital ulcers (DU) [2]. The Raynaud Condition Score (RCS), based on subjective information documented by patients in a diary, has been developed to assess RP in clinical trials [3].

In clinical practice, nailfold video capillaroscopy (NVC) is routinely used to assess morphologic changes to distinguish primary RP from secondary forms and follow SSc patients over time [4]. In NVC, it is, however, impossible to measure quantitative changes in the blood flow of affected fingers.

Raynaud's phenomenon is widespread in SSc patients, and treatment options, including vasodilating agents with different modes of action, are ineffective in a sizeable

number of patients [5]. Several non-invasive methods, including NVC, thermal imaging, and various Doppler ultrasound (US)-based techniques, have been described to assess the microvasculature [6]. However, these are cumbersome to perform, have relatively high costs, or require specialized equipment not readily available at most centers. Therefore, novel methods and applications that are widely available and easy to perform are required to assess functional blood flow changes in affected fingers.

1.1 Novel flow imaging techniques

Superb Micro Vascular Imaging (MVI) is a relatively novel US modality for flow imaging. In contrast to conventional Power Doppler (PD), MVI uses adaptive image analysis to achieve an increased low-velocity blood flow stability less dependent on motion artifacts [7]. In addition, MVI generates a high-resolution constant flow mapping of small vessels and related branches via an algorithm-driven suppression of interfering signals [8].

In rheumatology, MVI has been investigated to detect synovitis in patients with inflammatory arthritis, such as rheumatoid arthritis and juvenile idiopathic arthritis. In these diseases, MVI was more sensitive than conventional PD US in preliminary reports [9,10]. Potential advances of MVI may include a better follow-up of patients with minimal disease activity and the prediction or early recognition of disease flares [11]. Nevertheless, more extensive studies are lacking.

In this single-center feasibility trial, we prospectively analyzed a cohort of SSc patients using superb MVI as a method to detect and quantify digital blood flow compared to HCs.

2. Materials and Methods

2.1 Patient population

We consecutively recruited a convenience sample of ambulatory or hospitalized SSc patients from our center and healthy volunteers who served as a control group. Exclusion criteria for HCs were a history of primary or secondary RP, peripheral arterial occlusive disease, thromboembolism, diabetes mellitus, or cardiovascular events. All participants provided written informed consent according to the declaration of Helsinki. The Ethics committee of the University Medical Center Göttingen, Göttingen, Germany, approved the study protocol (protocol number 27/7/20).

2.2 Clinical data capture

General patient characteristics, such as age, sex, SSc type (VEDOSS [Very Early Diagnosis Of Systemic Sclerosis], limited or diffuse cutaneous) were documented. In addition, we recorded routine laboratory values and SSc-associated antibodies. Finally, we assessed all patients for the presence of SSc-related organ manifestations.

2.3 Ultrasound technique and settings

All examinations were performed on a *General Electric logiq E10* (GE Healthcare GmbH (Germany), Solingen, Germany) ultrasound machine equipped with a hockey stick probe (frequency 8 - 18 MHz). During the US scan, the individuals were seated upright and had the supinated, dominant hand on an examination pad in front of their body (Figure 1). The height of this pad was adjusted individually so that the arm was flexed about 90 – 120° at the elbow joint. The room temperature was constant at about 18 – 20° Celsius, and no participant had an apparent blood perfusion disturbance (e.g., RP attack) during the measurement.
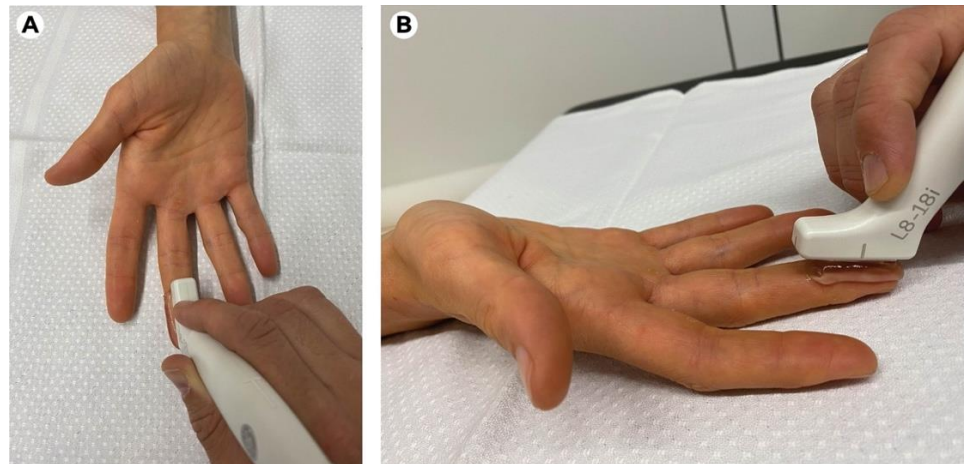
Figure 1. Patient and probe positioning for the ultrasound (US) scan. A. View from the examiner's perspective. B. Lateral view demonstrating probe positioning during the US scan. Note the very light pressure applied with the probe during the exam.

We performed both PD and MVI scans with a frequency of 12.5 MHz in all patients. For flow measurements, automated angle correction was used. For better visualization, Radiant*flow*™, an advanced visualization technology, which adds height and depth to color flow signals leading to a three-dimensional appearance of blood vessels, was set to the maximum (Figure 2). In addition, a standardized preset was created to provide the same measurement technique for all patients and controls. The assessment included the peak systolic flow (PS), the end-diastolic flow (ED), both reported in cm/s, and the resistance index (RI) of the examined vessels at the second to fifth fingers (DII – DV) of the dominant hand. Two different blood vessels were investigated on each finger, and the averages of the two measurements were used for the statistical analysis.
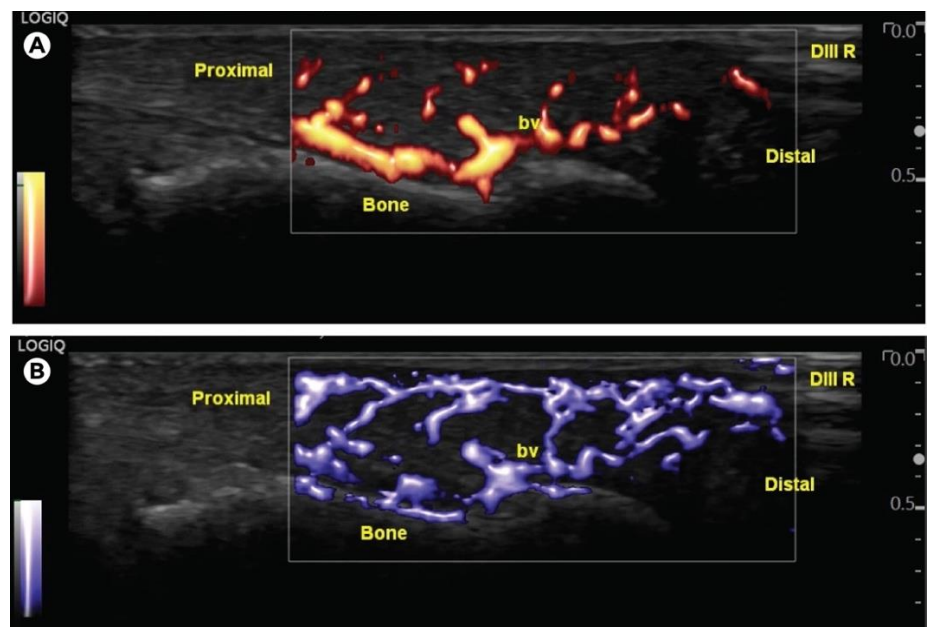

Figure 2. Demonstration of the anatomic structures of the fingertip in a healthy person. A. Power Doppler (PD) imaging. B. Micro Vascular Imaging (MVI). Note the superior visualization of superficial blood vessels and better continuity in panel B. bv, blood vessels; DIII, third digit; R, right.

2.3 Statistics

Demographic data were analyzed using descriptive statistics (median, range, and proportions). For flow velocity analysis, only MVI PS and ED values were used. Comparisons between groups were performed using a Welch's t-test, Mann-Whitney test, or Chi-square test. Effect sizes are reported with 95%-confidence intervals (CI). P-values <0.05 were considered statistically significant.

To establish an optimal cut-off value for each parameter to discriminate between HCs vs. SSc patients, receiver operator characteristics (ROC) curves were created, and the area under the curve (AUC) was calculated. Sensitivity and specificity were reported with 95% CI based on the cut-off point (Youden's J) that maximized Youden's index (according to the formula: sensitivity+specificity-1). Furthermore, the positive likelihood ratios (LR+) are reported.

Associations of PS and ED flow between fingers were analyzed by Pearson's correlation coefficient. Dependency of measurement variables in patients with SSc was assessed with linear regression, and the variance inflation factor (VIF) was calculated according to the formula $VIF=1/(1-R^2)$ to test for multicollinearity. Values greater than four, which are equivalent to an R^2 value of 0.75, were considered as evidence of multicollinearity, indicating redundant information.

All data analyses were performed with GraphPad Prism (version 9.2.0 for macOS, GraphPad Software, San Diego, California, USA), Microsoft Excel (version 16.52 for macOS, Microsoft Corporation, Redmond, WA, USA), STATA (version 17.0 for Windows, Stata Corp LLC, College Station, TX, USA).

3. Results

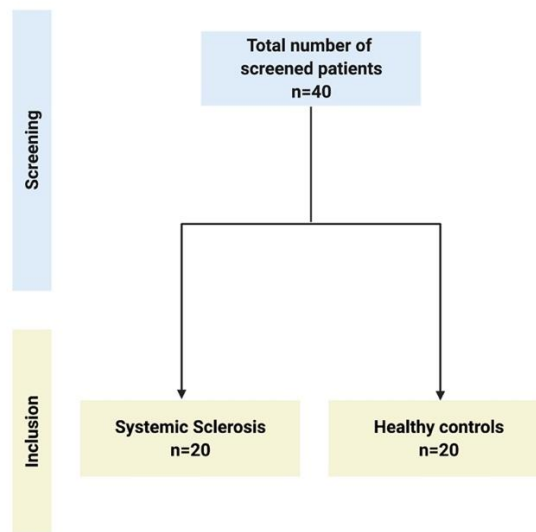*3.1. Baseline characteristics of Systemic Sclerosis patients and healthy controls*

Twenty healthy participants were examined. The median age was 26 years (range 19-56), and 13 (65%) were female. All were Caucasian; 19 (95%) participants were right-handed. All healthy individuals were nonsmokers. Two had arterial hypertension (10%) and were taking antihypertensive medication.

Twenty female SSc patients were included. The median age was 60 years (range 24-79). Nineteen patients (95%) were Caucasian, and one patient was of Asian descent (5%). All SSc patients were right-handed (100%). Figure 3 shows the disposition of patients and HCs.

SSc patients were significantly older than HCs (p<0.0001) and included more female participants (p=0.0083). Some of the recruited SSc patients were past (n=4, 20%) or current (n=2, 10%) smokers, while all HCs were non-smokers (p=0.0293). No differences were found regarding ethnicity or dexterity (p>0.9999).

Thirteen SSc patients were categorized as having limited cutaneous SSc (lcSSc), five with diffuse cutaneous SSc (dcSSc), one patient was diagnosed with Very Early Diagnosis of Systemic Sclerosis (VEDOSS). At the same time, one exhibited no skin involvement (*sine scleroderma*). Eighteen patients (90%) reported the presence of RP. Nailfold video capillaroscopy was available in 15 patients. Here, an "early pattern" was present in three patients while ten patients demonstrated an "active pattern" and two patients a "late pattern." Fourteen patients (70%) took vasoactive medication: Ten used calcium-channel blockers (CCB), seven patients received intravenous iloprost. In addition, a phosphodiesterase 5-inhibitor (PDE5-i) was prescribed in two SSc patients, and one patient was taking an endothelin receptor antagonist (ERA). All patient characteristics are shown in Table 1.

Figure 3. CONSORT flowchart of screened and included patients. n, number.

Table 1. Baseline characteristics of the study population.

	Systemic Sclerosis N=20	Healthy Controls N=20	p-value
Demographic data			
Age; years, median (range)	60 (24-79)	26 (19-56)	**<0.0001**
Female Sex, n (%)	20 (100%)	13 (65%)	**0.0083**
Right-handed	20 (100%)	19 (95%)	>0.9999
Disease duration; months, median (range)	50 (1-288)	-	-
Ethnicity			
- Caucasian, n (%)	19 (100%)	20 (100%)	>0.9999
- Asian, n (%)	1 (5%)	0 (0%)	
Smoking status			**0.0293**
- Current, n (%)	2 (10%)	0 (0%)	
- Past, n (%)	4 (20%)	0 (0%	
- Never, n (%)	14 (70%)	20 (100%)	
Systemic Sclerosis-related characteristics			
SSc type			
- VEDOSS, n (%)	1 (6.3%)	-	
- Limited, n (%)	13 (68.8%)	-	
- Diffuse, n (%)	5(18.8%)	-	
- Sine scleroderma, n (%)	1 (6.3%)	-	
Antibody status			
- Anti-Scl70., n (%)	2/19 (10.5%)	-	
- Anti-CENP-B, n (%)	12/19 (63.2%)	-	
- Anti-RNA Pol III, n (%)	3/15 (20%)	-	
- Anti-Fibrillarin pos., n (%)	2/17 (11.8%%)	-	
Organ manifestations			
- Raynaud's phenomenon, n (%)	18 (90%)	-	
- ILD, n (%)	6 (30%)	-	
- PAH, n (%)	3 (15%)	-	
- Gastrointestinal, n (%)	15 (75%)	-	
- Musculoskeletal, n (%)	19 (95%)	-	

- Renal, n (%)	4 (20%)	-

Nailfold video capillaroscopy		
- Early pattern, n (%)	3/15 (20%)	-
- Active pattern, n (%)	10/15 (66.6%)	-
- Late pattern, n (%)	2/15 (13.3%)	-
- Normal findings, n (%)	0 (0%)	-
Current treatment		
- Prednisolon, n (%)	7/19 (36.8%)	-
- MMF, n (%)	3/19 (15.8%)	-
- MTX, n (%)	2/18 (11.1%)	-
Vasoactive medications		
- CCB	10/18 (55.6%)	-
- Iloprost	7/19 (36.9%)	-
- ERA	1/19 (5.2%)	-
- PDE-5i	2/19 (10.5%)	-

CCB, calcium channel blocker; CENP-B, centromere protein B; ERA, endothelin receptor antago-nist; HC, Healthy Control; ILD, interstitial lung disease; MMF, mycophenolate mofetil; MTX, methotrexate; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase-5 inhibitor; RNA Pol, ribonucleic acid polymerase; SSc, Systemic Sclerosis; VEDOSS, Very Early Diagnosis of Systemic Sclerosis. Bold indicates statistically significant p-values.

3.2. Comparison of flow velocity in patients with Systemic Sclerosis and healthy controls

Microvascular imaging was performed in all SSc patients and HCs on DII-V, respectively. Since SSc patients were significantly older than HCs, we analyzed the PS and ED flow velocities in relation to age (Figure 4). No correlation with age was found, neither in HCs (Figure 4A, $r^2=0.03$ for PS flow, $r^2=0.18$ for ED flow), nor in SSc patients (Figure 4B, $r^2=0.08$ for PS flow, $r^2=0.01$ for ED flow).
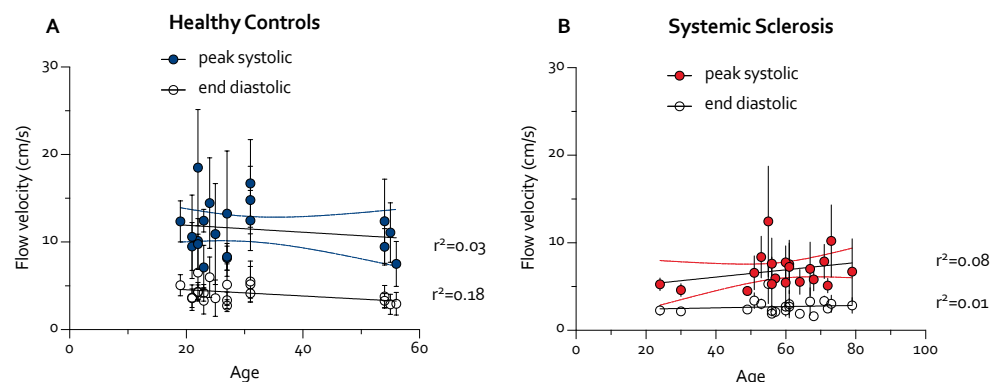

Figure 4. A. Peak systolic and end-diastolic flow velocity measurements of healthy controls in relation to age. B. Peak systolic and end-diastolic flow velocity measurements of Systemic Sclerosis patients in relation to age.

Next, flow velocities of all fingers (Figure 5) and each finger separately were compared between the two groups (Figure 6). It was shown that both PS flow velocity and ED flow velocity were significantly different between the two groups. For all fingers measured, the difference of the medians (Δ) for PS velocity was 4.675 cm/s (95% CI 3.3-5.25, p<0.0001), for ED velocity 1.375 cm/s (95% CI 0.85-1.65, p<0.0001) (Figure 5).
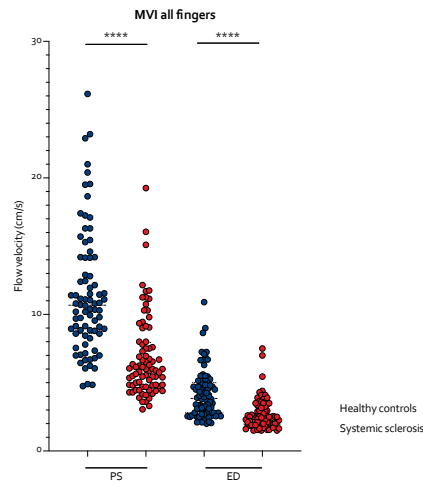
Figure 5. Flow velocity measurements on microvascular imaging of all fingers combined. The median peak systolic (PS) and end-diastolic (ED) flow velocity measurements of healthy controls (blue) are significantly higher compared to Systemic Sclerosis patients (red). ****p<0.0001. MVI, microvascular imaging.

For the individual fingers, the Δ of medians for PS velocity were 5.225 cm/s (95% CI 2.95-7.5, p<0.0001), and 2.325 (95% CI 1.1-3.1, p<0.0001) for ED flow velocitiy for DII (Figure 6A); for PS flow velocitiy 4.975 cm/s (95% CI 1.15-6.15, p<0.01), and for ED flow velocitiy 1.4 cm/s (95% CI 0.15-1.9, p<0.05) at DIII (Figure 6B); for DIV, Δ of the median for PS velocity was 5.275 cm/s (95% CI 2.5-6.8, p<0.0001), and 1.05 cm/s (95% CI 0.4-2.4, p<0.01) for ED flow velocity (Figure 6C). Finally, Δ of the median for PS velocity at DV was 3.325 cm/s (95% CI 2.2-5, p<0.001), and 0.875 cm/s (95% CI 0.6-1.6, p<0.001) for ED flow velocity (Figure 6D).

Figure 6. Flow velocity measurements on microvascular imaging in healthy controls (blue) vs. Systemic Sclerosis patients (red) were measured in the second (A), third (B), fourth (C), and fifth (D) fingers, respectively. Flow velocities are significantly higher in HC. ****p<0.0001, ***p<0.001, **p<0.01, *p<0.05. PS, peak systolic; ED, end-diastolic.

3.3. *Determination of cut-off values to discriminate healthy controls from Systemic Sclerosis*

To determine which values of flow velocity are discriminative between HCs and SSc

patients, receiver operating characteristics (ROC) curves were created. Different measurements were calculated, which are summarized in Table 2: Cut-off points and test characteristics were calculated for all fingers combined, each finger, minimum and maximum values, as well as the sum of measured values. Overall, the best sensitivity, specificity, and LR+ were obtained for the minimum value measured value per finger (Figure 7). For PS flow velocity, an optimal cut-off point of <6.13 cm/s showed excellent sensitivity (0.90, 95% CI 0.70-0.98) and specificity (0.85, 95% CI 0.64-0.95), corresponding to an LR+ of 6.0. For ED flow velocity, similar test characteristics were obtained. The optimal cut-off point was estimated at <2.13 cm/s, sensitivity was 0.85 (95% CI 0.64-0.95), specificity was 0.80 (95% CI 0.58-0.92), corresponding to a LR+ of 4.25.

Of note, for the end-diastolic flow measurements, the best test properties were observed for the maximum value measured (Table 2). Nevertheless, the best overall area under the curve (AUC) was observed for the minimum values of each finger.

Table 2. Test characteristics and optimal cut-off points for all fingers.

	All fingers combined	Minimum	Maximum	Sum of values
Sens PS (95% CI)	0.69 (0.58-0.78)	**0.90 (0.70-0.98)**	0.90 (0.70-0.98)	0.85 (0.64-0.95)
Spec PS (95% CI)	0.88 (0.79-0.93)	**0.85 (0.64-0.95)**	0.70 (0.48-0.85)	0.90 (0.70-0.98)
Sens ED (95% CI)	0.65 (0.54-0.75)	0.85 (0.64-0.95)	**0.90 (0.70-0.98)**	0.80 (0.58-0.92)
Spec ED (95% CI)	0.80 (0.70-0.87)	0.80 (0.58-0.92)	**0.95 (0.76-1.0)**	0.85 (0.64-0.95)
AUC PS (95% CI)	0.84 (0.77-0.90)	**0.93 (0.85-1.0)**	0.85 (0.73-0.96)	0.91 (0.82-1.0)
AUC ED (95% CI)	0.80 (0.73-0.87)	**0.90 (0.80-0.99)**	0.92 (0.82-1.0)	0.89 (0.79-0.99)
LR+ PS	5.5	**6.0**	3.0	8.5
LR+ ED	3.3	4.24	**18.0**	5.3
Youden's J PS	<6.9 cm/s	**<6.13 cm/s**	<12.28 cm/s	<32.1 cm/s
Youden's J ED	<2.68 cm/s	<2.13 cm/s	**<4.45 cm/s**	<12.65 cm/s

CI, confidence interval; D, digit; ED, end-diastolic; LR+, positive likelihood ratio; PS, peak systolic, Sens, sensitivity; Spec, specificity. Bold indicates the best values obtained.
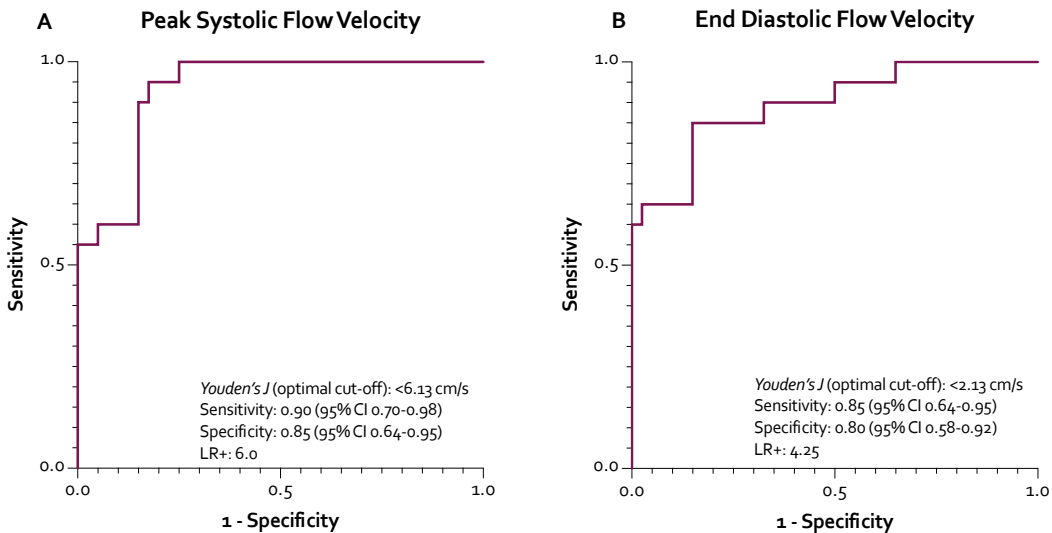

Figure 7. Receiver operating characteristics curve for PS and ED flow velocities for the minimum values obtained. A. Cut-off and test characteristics for PS flow velocity. B. Cut-off and test characteristics for ED flow velocity. LR+, positive likelihood ratio.

3.4 Correlation of flow velocity in different fingers

To test for the correlation of the measured values in each finger in HCs and SSc patients, we performed a correlation analysis of fingers DII-DV (Figure 8). Correlation

between the different fingers was, despite being statistically significant at D II/III in SSc patients and D II/IV and D IV/V in HCs, at best moderate. The highest correlation in SSc patients for PS and ED flow was observed for the second and third finger (correlation co-efficient of 0.58 and 0.65, respectively). In HCs, the highest correlation was observed for PS flow between the second and fourth finger and between the fourth and fifth finger (correlation coefficients of 0.57 and 0.54, respectively).
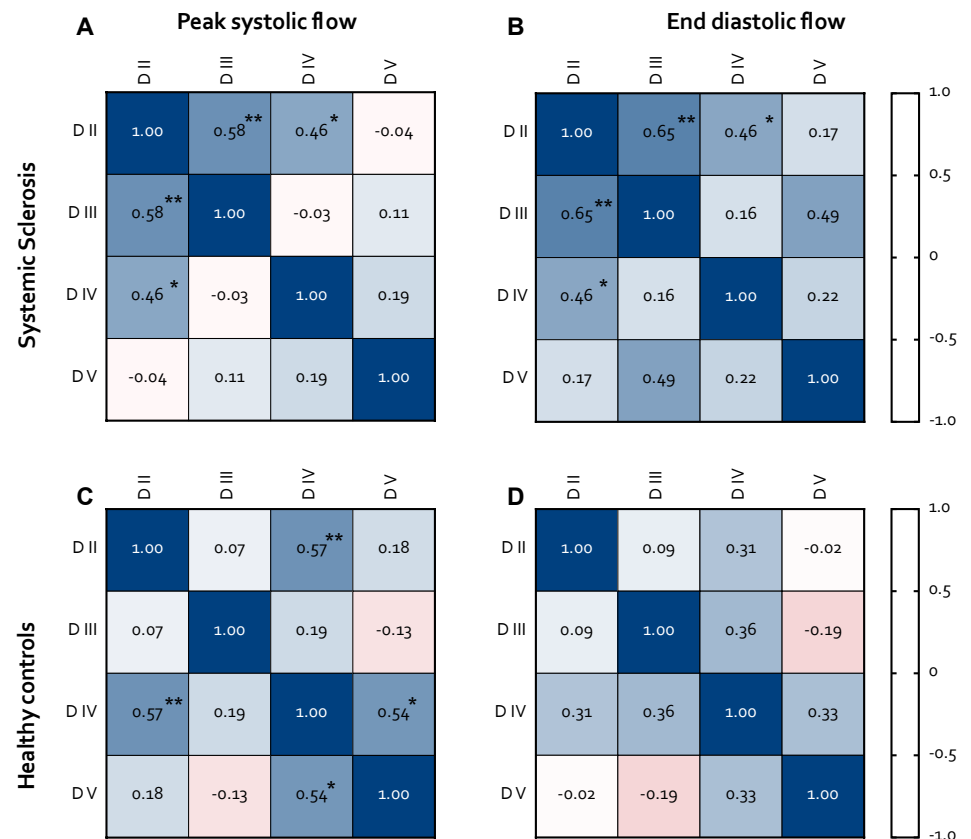

Figure 8. Correlation matrix showing correlation coefficients for peak systolic and end-diastolic flow velocity in different fingers for Systemic Sclerosis patients (panels A and B) and healthy controls (panels C and D). **p<0.01, *p<0.05. D, digit.

3.5   *Linear regression of individual fingers in Systemic Sclerosis*

Lastly, we performed a linear regression and calculated the variance inflation factor (VIF) to test whether one or more fingers could be omitted during the US exam. Table 3 shows that neither values for PS flow velocity nor ED flow velocity explained the values of other fingers assessed. All R^2 values with each finger as dependent variable was below 0.7.

Table 3. Variance inflation factor for individual fingers in SSc patients after linear regression.

	D II	D III	D IV	D V
Peak Systolic				
VIF	1,69	1,18	1,49	1,09
End-diastolic				
VIF	2,58	2,66	1,48	1,54

D, digit; VIF, variance inflation factor.

4. Discussion

The present study is the first to investigate digital MVI in healthy subjects and patients with SSc. Since our healthy control group exhibited almost no confounding comorbidities, it was well suited to define normal values of MVI and determine cut-off values to discern them from SSc patients. In addition, although HCs were significantly younger than the SSc patients, age did not have a relevant influence on the digital flow velocities. Finally, systemic Sclerosis patients showed higher use of vasodilating agents, potentially influencing flow measurements. Nevertheless, despite using these drugs, SSc patients had consistent and significantly lower values than HCs.

Our results further indicate that all four fingers should be assessed since there was only a weak to moderate correlation between individual fingers. As this was also true for HCs, it seems to be an inherent characteristic of MVI measurements. There were measurements in some fingers that correlated moderately well and yielded statistically significant results. However, the regression models obtained did not provide evidence of multicollinearity, indicating that all fingers need to be examined. Nevertheless, this must be tested in a larger sample. Finally, the MVI with flow measurements performed on four fingers took less than 15 minutes, which is, in our view, feasible in clinical practice.

Overall, due to the excellent visualization of microvascular tissue and organ perfusion, MVI has the potential to avoid invasive or radiation-assisted examinations. Still, more extensive studies in rheumatic conditions are not available. In our experience, visualization with MVI was better suited for superficial blood vessels than conventional PD US. Some examination modalities, such as thermography and others, are already available for SSc [12]. However, these are not available everywhere; some are cumbersome to perform, expensive, or require additional equipment. The advantage of MVI is that rheumatologists are already used to performing US examinations and would need only an additional software application to use MVI.

Our study has several limitations: The study cohort included relatively few individuals. However, it included a representative sample of SSc patients. Currently, we cannot ascertain if there are differences between different diseases, such as mixed connective tissue disease or systemic lupus erythematosus, which frequently show RP. Furthermore, based on the presented results, we cannot claim the superiority of MVI to PD US. Both open questions will be assessed in an extension of the presented study. Finally, based on our results, we cannot recommend estimating flow velocity in less than all four fingers.

The strengths of our study are the feasibility of MVI in clinical practice, the relatively short examination time required, and the novelty of the presented data. Thus, MVI may offer potential applications in assessing microvascular alterations in patients with inflammatory rheumatic diseases, such as SSc and others.

5. Conclusions

We present the first study of the use of MVI as a novel imaging technique to measure blood flow velocity in patients with SSc. For the first time, we report the method's feasibility and cut-off points to discriminate healthy controls from SSc patients. Whether the results of MVI correlate with organ manifestations or vascular complications of SSc needs to be tested in a larger cohort.

References

1. Allanore, Y.; Simms, R.; Distler, O.; Trojanowska, M.; Pope, J.; Denton, C.P.; Varga, J. Systemic Sclerosis. *Nat Rev Dis Primers* **2015**, *1*, 15002, doi:10.1038/nrdp.2015.2.

2. Gabrielli, A.; Avvedimento, E.V.; Krieg, T. Scleroderma. *N. Engl. J. Med.* **2009**, *360*, 1989–2003, doi:10.1056/NEJMra0806188.

3. Wigley, F.M.; Wise, R.A.; Seibold, J.R.; McCloskey, D.A.; Kujala, G.; Medsger, T.A.; Steen, V.D.; Varga, J.; Jimenez, S.; Mayes, M.; et al. Intravenous Iloprost Infusion in Patients with Raynaud Phenomenon Secondary to Systemic Sclerosis. A Multicenter, Placebo-Controlled, Double-Blind Study. *Ann. Intern. Med.* **1994**, *120*, 199–206.

4. Lambova, S.N.; Müller-Ladner, U. Nailfold Capillaroscopy in Systemic Sclerosis – State of the Art: The Evolving Knowledge about Capillaroscopic Abnormalities in Systemic Sclerosis. *Journal of Scleroderma and Related Disorders* **2019**, *4*, 200–211, doi:10.1177/2397198319833486.

5. Khouri, C.; Lepelley, M.; Bailly, S.; Blaise, S.; Herrick, A.L.; Matucci-Cerinic, M.; Allanore, Y.; Trinquart, L.; Cracowski, J.-L.; Roustit, M. Comparative Efficacy and Safety of Treatments for Secondary Raynaud's Phenomenon: A Systematic Review and Network Meta-Analysis of Randomised Trials. *The Lancet Rheumatology* **2019**, *1*, e237–e246, doi:10.1016/S2665-9913(19)30079-7.

6. Cutolo, M. Detection of Microvascular Changes in Systemic Sclerosis and Other Rheumatic Diseases. 13.

7. Deegan, A.J.; Wang, R.K. Microvascular Imaging of the Skin. *Phys. Med. Biol.* **2019**, *64*, 07TR01, doi:10.1088/1361-6560/ab03f1.

8. Artul, S.; Nseir, W.; Armaly, Z.; Soudack, M. Superb Microvascular Imaging: Added Value and Novel Applications. *J Clin Imaging Sci* **2017**, *7*, 45, doi:10.4103/jcis.JCIS_79_17.

9. Alis, D.; Erol, B.C.; Akbas, S.; Barut, K.; Kasapcopur, O.; Adaletli, I. Superb Microvascular Imaging Compared With Power Doppler Ultrasound in Assessing Synovitis of the Knee in Juvenile Idiopathic Arthritis: A Preliminary Study. *Journal of Ultrasound in Medicine* **2020**, *39*, 99–106, doi:10.1002/jum.15079.

10. Lee, G.Y.; Kim, S.; Choi, S.T.; Song, J.S. The Superb Microvascular Imaging Is More Sensitive than Conventional Power Doppler Imaging in Detection of Active Synovitis in Patients with Rheumatoid Arthritis. *Clin Rheumatol* **2019**, *38*, 2613–2620,

doi:10.1007/s10067-019-04550-0.

11.   Almeida, D.E.; Costa, E.; Cerqueira, M. Advances in Ultrasound Imaging in Rheumatology—What Do They Mean and What Challenges Do They Pose? The Example of Microvascular Imaging. *Journal of Ultrasound in Medicine n/a*, doi:10.1002/jum.15754.

12.   Cutolo, M.; Smith, V. Detection of Microvascular Changes in Systemic Sclerosis and Other Rheumatic Diseases. *Nat Rev Rheumatol* **2021**, *17*, 665–677, doi:10.1038/s41584-021-00685-0.