Rheumatology Advance Access published December 20, 2011

RHEUMATOLOGY

Original article

doi:10.1093/rheumatology/ker414

Ulnar artery occlusion is predictive of digital ulcers in SSc: a duplex sonography study

Marc Frerix[1,2], Johannes Stegbauer[3], Duska Dragun[4], Alexander Kreuter[5] and Stefan M. Weiner[2]

Abstract

Objectives. To assess the prevalence and risk factors of ulnar artery occlusion (UAO) in an unselected SSc patient cohort and to determine whether UAO is associated with digital ulcers (DUs).

Methods. A total of 79 SSc patients and 40 'healthy' controls underwent colour duplex sonography of the radial and ulnar artery to compare blood flow velocity, resistive indices (RIs) and presence of occlusion and were followed for a mean of 53 months.

Results. In both, radial and ulnar arteries, peak systolic velocity (PSV) and end-diastolic velocity (EDV) were significantly lower and RI higher in SSc patients compared with controls (PSVrad: 40.1 *vs* 48.6 cm/s; PSVuln 38.2 *vs* 56.6 cm/s; EDVrad 3.8 *vs* 10.4 cm/s; EDVuln 3.0 *vs* 13.0 cm/s; RIrad 0.91 *vs* 0.82; RIuln 0.92 *vs* 0.80; all $P < 0.01$). Seventeen (21.5%) SSc patients had UAO (11 patients bilateral) compared with none in the control subjects. Patients with UAO had a significantly longer disease duration (170 *vs* 66 months, $P < 0.001$). At baseline, the prevalence of DU was not different in upper extremities with UAO [8/28 (28.6%)] compared with upper extremities without UAO [36/129 (27.9%)]. However, during follow-up new or recurrent DU occurred more often in upper extremities with UAO than in those without UAO [14/28 (50%) *vs* 24/113 (21.2%); relative risk (RR) = 2.4; 95% CI 1.4, 3.7; $P = 0.002$].

Conclusion. Blood flow is significantly decreased in radial and ulnar arteries in SSc. UAO is frequent and an important risk factor for the development of DUs in patients with SSc.

Key words: SSc, scleroderma, duplexsonography, US, ulnar artery, digital ulcers, vascular disease, endothelin-1 type A receptor autoantibodies, angiotensin II type 1 receptor autoantibodies

Introduction

Microvascular disease is common and has been investigated intensively in SSc patients. However, only a few studies investigated the occurrence of macrovascular changes of peripheral artery disease [1–15]. In 1998, Stafford *et al.* [1] reported a high frequency of ulnar artery involvement (10/19 patients presented with smooth thickening of the ulnar arterial wall). Although atherosclerosis may also present as 'smooth wall thickening' in US examination [16], the authors concluded that the lesions are of non-atherosclerotic origin, as the upper limbs did not show any similar alterations. Later, Taylor *et al.* [2] reported that intimal fibrosis and narrowing of the lumen are consistent with the histological changes observed in microvascular disease. Taken together, these findings of peripheral ulnar artery disease in SSc suggest a non-atherosclerotic vasculopathy.

To date, the general prevalence of ulnar artery occlusion (UAO) in SSc is still unclear. In addition, it is unkown whether there are associations of ulnar artery disease and traditional cardiovascular risk factors, specific autoantibodies, skin thickening as assessed by modified Rodnan skin score (mRSS), disease duration or disease subset. Moreover, several questions had not yet been addressed, including the association with fingertip ulcers and

[1]Department of Internal Medicine and Rheumatology, Division of Rheumatology and Clinical Immunology, Justus-Liebig-University of Giessen, Kerckhoff-Clinic Bad Nauheim, [2]Department of Nephrology and Rheumatology, Krankenhaus der Barmherzigen Brüder, Teaching Hospital of the University of Mainz, Trier, [3]Department of Internal Medicine and Nephrology, Heinrich-Heine-University Düsseldorf, Düsseldorf, [4]Department of Nephrology and Intensive Care Medicine, Charité University Hospital, Berlin and [5]Department of Dermatology, Venerology and Allergology, University of Bochum, St Josef-Hospital Bochum, Germany

Submitted 13 June 2011; revised version accepted 1 November 2011.

Correspondence to: Marc Frerix, Kerckhoff-Clinic Bad Nauheim, Department of Internal Medicine and Rheumatology, Benekestr. 2-8, 61231 Bad Nauheim, Germany. E-mail: m.frerix@kerckhoff-klinik.de

haemodynamic parameters. Recently Riemekasten *et al.* [17] reported on the role of endothelin-1 type A receptor (ET_AR) and against angiotensin II type 1 receptor (AT_1R) autoantibodies in SSc. These autoantibodies seem to be associated with several SSc-related manifestations [development of digital ulcers (DUs), pulmonary artery hypertension, lung fibrosis], and high antibody levels predicted disease-related mortality. However, involvement of autoantibodies in the development of UAO has not been investigated.

Thus the aim of the present study was to evaluate the prevalence of ulnar artery involvement in a cohort of unselected patients with SSc and their predictive value for the recurrence or new onset of DU, and to compare findings with traditional risk factors for atherosclerosis and autoantibody profiles.

Patients and methods

Patients

Between January 2005 and June 2006, 80 consecutive patients with the diagnosis of SSc and 40 healthy volunteers underwent colour-coded duplex sonography (CDS) examination of radial and ulnar arteries. Patients were recruited from the Department of Dermatology, Venerology, and Allergology, University of Bochum, St Josef-Hospital Bochum, and CDS examination was performed in the Department of Nephrology and Rheumatology, Marienhospital Herne, University of Bochum (M.F., J.S. and S.M.W.). A total of 79 patients fulfilled the preliminary classification criteria for SSc of the American Rheumatism Association [18] and were subclassified in the respective subsets (45 patients with lcSSc and 34 patients with dcSSc) according to the criteria reported by LeRoy *et al.* [19, 20].

Written informed consent was obtained from all patients before entry into the study, according to the Declaration of Helsinki and guidelines of the local ethics committee of the Ruhr-University Bochum. All patients were enrolled into the German Systemic Sclerosis Network Register (DNSS). A vote by the local ethics committee of the Ruhr-University Bochum was given for the whole study group on the basis of a registry in the DNSS.

Detailed characteristics of patients and controls are given in Table 1. A total of 314 radial and ulnar arteries of 79 SSc patients were evaluated. In one scleroderma patient, the data of left radial and ulnar artery examination were lost. Overall, 160 radial and ulnar arteries of 40 healthy subjects served as controls.

CDS

To avoid the presence of RP, US examination measurements of patients were performed with a moderately preheated US gel and after a minimum of 20 min acclimatization in our US laboratory at a room temperature of at least 24–26°C. Assessment of angle-adjusted radial and ulnar artery flow velocity was performed at the wrist in all patients and controls. If measurement was not possible with a standard angle $<60^\circ$, flow velocity values were not taken for statistical evaluation. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were determined for the calculation of the resistive index: resistive index (RI) = (PSV − EDV)/PSV. US measurements were performed by using the Acuson Sequoia 512 US system equipped with an 8L5 and 15L8w linear transducer or by using Acuson X300 equipped with a VF 10-5 linear transducer.

Assessment of DUs, cardiovascular risk factors and autoantibodies

A history of DUs was recorded at baseline and during follow-up, including fingertip ulcers, pitting scars, ulcers over the MCP, proximal and DIP joints and ulcers associated with calcinosis. Patients with current DUs were usually followed up in intervals of 3–6 months and patients without DU were evaluated every 6–12 months at the Department of Dermatology, Venerology, and Allergology, University of Bochum. Patients who missed a regular visit were interviewed by telephone. Additionally, a review of patient health records was performed.

To identify risk factors associated with reduced radial or ulnar artery flow velocity and UAO, the following parameters were assessed: age, sex, BMI, history of arterial hypertension, use of anti-hypertensive drugs, blood pressure levels (mean of left and right brachial artery measurement after at least 5 min rest), history of diabetes mellitus, smoking (current or former and pack-years), history of coronary heart disease, age at diagnosis, disease duration since date of SSc diagnosis and mRSS. Routine laboratory assessment at baseline included blood cell count, cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride, complement (C3, C4), CRP and serum creatinine. ANAs were tested by standard IF test using Hep2 cells. Antibodies against Scl-70, centromere, U1RNP, Pm-Scl and aPLs (cardiolipin IgG and IgM, β1-glycoprotein1 IgG and IgM) were tested by ELISA (Euroimmune, Lübeck, Germany). Anti-ET_AR antibody units and anti-AT_1R antibody units were tested by ELISA (CellTrend GmbH Luckenwalde, Germany) as described previously [17].

Arterial hypertension was defined by blood pressure >140/90 mmHg or by the use of anti-hypertensive drugs. Dyslipidaemia was defined by elevated plasma cholesterol (>200 mg/dl for age 18–29 years; >220 mg/dl for age 30–40 years; >240 mg/dl for age >40 years), plasma LDL cholesterol (>160 mg/dl) and/or plasma triglyceride (>200 mg/dl) levels, or use of lipid-lowering drugs like HMG co-inhibitors [21, 22]. Plasma HDL cholesterol levels have been assessed as protective vascular factor.

Statistical methods

For comparison of scale variables, we used unpaired or paired two-sided Student's *t*-test. Pearson correlation was used to assess possible associations between radial and ulnar artery flow velocity values and scale variables. In cases of non-normally distributed variables, we used Mann–Whitney U-test. Normal distribution was

Table 1 Characteristics of patients and controls

Characteristic	lcSSc ($n = 45$)	dcSSc ($n = 34$)	Controls ($n = 40$)
Age, mean (S.D.), years	63.8 (11.0)	49.4 (13.7)	49.2 (5.8)
Female, *n* (%)	42 (93.3)	28 (82.4)	29 (72.5)
BMI, mean (S.D.), kg/m^2	25.2 (4.2)	23.7 (4.2)	25.6 (4.2)
Hypertension, *n* (%)	24 (53.3)	7 (20.6)	5 (12.5)
Smoking (current or former), *n* (%)	19 (42.2)	21 (61.8)	13 (32.5)
Diabetes, *n* (%)	3 (6.7)	0 (0)	2 (5)
Dyslipidaemia, *n* (%)	26 (57.8)	18 (52.9)	7 (17.5)
Mean RSS (median)	8.74 (6.5)	14.21 (12)	NA
Age at diagnosis, mean (S.D.), years	54.8 (13.8)	42.9 (13.6)	NA
Disease duration, mean (S.D.), months	100.4 (112.8)	72.1 (74.7)	NA
RP, *n* (%)	43 (95.6)	30 (88.2)	None
DUs, *n* (%)	15 (33.3)	11 (32.4)	None
Affected hands, *n* (%)	23/90 (25.6)	21/68 (30.9)	None
Pulmonary arterial hypertension, *n* (%)	10 (22.2)	5 (14.7)	None
Scleroderma renal crisis	None	None	NA
ANA, *n* (%)	43 (95.6)	34 (100)	NA
SCL-70 antibody	4 (8.9)	20 (58.8)	NA
Centromere antibody, *n* (%)	32 (71.1)	1 (2.9)	NA
U1RNP antibody, *n* (%)	0 (0)	1 (2.9)	NA
Pm-Scl antibody, *n* (%)	2 (4.4)	1 (2.9)	NA
aPLs	2 (4.4)	3 (8.8)	NA
Anti-ET_AR antibody (cut-off 10.4), *n* (%)	14/43 (32.6)	17/33 (51.5)	NA
Anti-AT_1R antibody (cut-off 9.5), *n* (%)	21/43 (48.8)	17/33 (51.5)	NA

NA: not applicable.

tested by Q–Q plots. For comparison of categorical variables, we used chi-square test or in the case of non-confirmed conditions Fisher's exact test. ROC analysis was performed for anti-AT_1R antibody and anti-ET_AR antibody levels predictive of UAO. In cases of multiple testing, a Bonferroni correction was used: six tests were performed to compare radial and ulnar artery flow between patients and controls and disease subsets; $P = 0.008$ was considered statistically significant. Thirty-seven tests were performed to assess potential associated parameters with UAO in patients; $P = 0.001$ was considered statistically significant. Statistical analysis was performed using PASW Statistics, version 18.

Results

Comparison of study patient and control characteristics

In our cohort, lcSSc patients were older than dcSSc patients more often had arterial hypertension, had longer disease duration and were less often smokers. Notably, there was no difference in the frequency of DUs. Five patients were positive for both centromere antibody and anti-topo antibody (SCL-70). Detailed characteristics of patients and controls are given in Table 1.

Comparison of blood flow in radial and ulnar arteries

Mean PSV was significantly lower in both the radial and ulnar artery in SSc patients compared with controls. EDV was also significantly lower and RI was significantly higher in SSc patients compared with controls (Table 2). No significant difference in radial and ulnar artery flow was detected between lcSSc and dcSSc patients (Table 3). In our SSc patient cohort, the mean ulnar artery blood flow was not different from that measured in the radial artery (38.8 *vs* 40.1 cm/s, $P = 0.550$). In contrast, in healthy controls we found a significantly higher mean blood flow in ulnar arteries compared with radial arteries (57.0 *vs* 48.6 cm/s, $P = 0.004$).

Association of ulnar and radial artery blood flow with DU and possible risk factors

In healthy controls, there was no association between sex, age, BMI, hypertension and nicotine abuse with radial or ulnar artery flow. Female patients had a lower radial artery blood flow than male patients (38.1 *vs* 56.5 cm/s, $P = 0.003$), but there was no significant difference in ulnar artery blood flow (37.0 *vs* 45.8 cm/s, $P = 0.481$). In SSc patients, BMI, nicotine abuse, disease duration, RSS and the presence of DUs at baseline were not associated with mean radial or ulnar artery blood flow. Formally, Pearson correlation analysis showed a weak association between age and radial artery PSV ($r = 0.350$, $P = 0.004$), but none with ulnar artery PSV ($r = 0.255$, $P = 0.061$). There was no significant difference in baseline radial or ulnar artery flow between patients' hands with and without DUs during follow-up (PSVrad 45.3 *vs* 37.7 cm/s, $P = 0.104$; PSVuln 30.4 *vs* 38.6 cm/s, $P = 0.077$).

Table 2 Comparison of CDS parameters between scleroderma patients and healthy subjects

Parameter	SSc patients ($n = 79$)	Controls ($n = 40$)	*P*-value
Radial artery			
PSV, cm/s	40.1 (15.6)	48.6 (13.4)	0.006*
EDV, cm/s	3.8 (4.7)	10.4 (8.3)	<0.001*
RI	0.91 (0.09)	0.82 (0.12)	<0.001*
Ulnar artery			
PSV, cm/s	38.2 (15.8)	56.6 (17.8)	<0.001*
EDV, cm/s	3.0 (3.8)	13.0 (10.8)	<0.001*
RI	0.92 (0.07)	0.80 (0.14)	<0.001*

Values are mean (S.D.). *Statistically significant after Bonferroni correction.

Table 3 Comparison of CDS parameters between lcSSc and dcSSc patients

Parameter	lcSSc ($n = 45$)	dcSSc ($n = 34$)	*P*-value
Radial artery			
PSV, cm/s	41.0 (14.7)	38.9 (16.9)	0.586
EDV, cm/s	3.9 (4.9)	3.7 (4.5)	0.856
RI	0.92 (0.09)	0.91 (0.09)	0.435
Ulnar artery			
PSV, cm/s	39.7 (13.0)	36.0 (19.0)	0.435
EDV, cm/s	2.8 (4.4)	3.3 (2.9)	0.611
RI	0.92 (0.08)	0.91 (0.06)	0.488

Values are mean (S.D.). *Statistically significant after Bonferroni correction.

Frequency of UAO in scleroderma and healthy controls

At baseline, 17 (22%) of 79 patients with SSc had UAO. In these, bilateral UAO was observed in 11 (65%) SSc patients. UAO was observed more frequently in lcSSc than dcSSc patients, but without statistical significance (28.9 *vs* 11.8%, $P = 0.097$). However, the overall number of occluded ulnar arteries was significantly higher in lcSSc [22/90 (24.4%) ulnar arteries] than dcSSc [6/67 (9.0%) ulnar arteries, $P = 0.012$]. No occlusion of the radial artery was detected in our patient cohort. Neither ulnar nor radial artery occlusion was detected in our control subjects.

Influence of UAO on ipsilateral radial blood flow in SSc patients

The ipsilateral radial artery flow was not increased in upper extremities with UAO compared with upper extremities without UAO (39.0 ± 13.6 *vs* 39.1 ± 16.4 cm/s, $P = 0.973$). Of note, no UAO could be observed in our control group. However, in one control subject we found a right-sided hypoplastic ulnar artery with decreased blood flow (11 cm/s, compared with 36.1 cm/s left sided) and a compensatory increased blood flow in the ipsilateral radial artery (95.4 cm/s, compared with 40.0 cm/s left sided).

Association of UAO with potential risk factors

Patients with UAO had a significantly longer disease duration compared with patients without UAO (170 *vs* 65.8 months; $P = 0.001$ in univariate analysis; $P < 0.001$ in multivariate analysis adjusted for age, age at time of diagnosis and limited cutaneous involvement). In contrast, typical illness-related antibodies, centomere antibody and anti-topo antibody (SCL-70) were not statistically associated with UAO.

Traditional cardiovascular risk factors, other tested laboratory parameters and autoantibodies were not associated with the occurrence of UAO (Table 4). Also, antihypertensive medication and current or former use of immunosupressive drugs as well as cumulative doses of immunosuppressive drugs such as prednisone, HCQ, AZA or CYC were not associated with UAO (data not shown).

Subanalysis of radial and ulnar artery flow in patients with short disease duration

Forty patients (19 lcSSc, 21 dcSSc) had a disease duration of less than 5 years (mean 19 months, range 0–56 months; 12 patients were enrolled at the time of first diagnosis).

In this subgroup of patients with short disease duration, mean PSV and EDV were also significantly lower and RI higher compared with controls (PSVrad 39.7 *vs* 48.6 cm/s, $P = 0.017$; PSVuln 38.3 *vs* 56.6 cm/s; EDVrad 3.2 *vs* 10.4 cm/s; EDVuln 2.4 *vs* 13.0 cm/s; RIrad 0.93 *vs* 0.82; RIuln 0.92 *vs* 0.80; all $P < 0.001$). Five UAOs were observed in three patients with disease durations of 0 (unilateral), 30 and 53 months (both bilateral UAO).

Association of UAO with DUs

At the initial visit, DUs were present in 44 SSc patients' upper extremities: in 8/28 (28.6%) upper extremities with UAO as compared with 36/129 (27.9%) upper extremities without UAO ($P = 0.943$). During the follow-up [available for 71/79 (89.9%) patients, mean 53 months], new or recurrent DUs developed more frequently in upper extremities with than without initially diagnosed UAO [14/28 (50%) *vs* 24/113 (21.2%); RR = 2.4; 95% CI 1.4, 3.7; $P = 0.002$; Fig. 1].

Association of UAO with number and subtype of DU

At baseline, 19 DU were observed in 28 hands with UAO compared with 67 DU in 129 hands without UAO [mean 0.7 *vs* 0.5 per hand; relative risk (RR) = 1.3; 95% CI 0.9, 1.7; $P = 0.125$]. During follow-up, the number of new or recurrent DUs was significantly higher in hands with UAO (34 ulcers in 28 hands, mean 1.2 per hand) compared with hands without UAO (50 ulcers in 113 hands, mean 0.44 per hand; RR = 2.7; 95% CI 1.8, 4.1; $P < 0.001$).

Out of 34 DUs during follow-up in hands with UAO, 25 (73.5%) were fingertip ulcers, 5 (14.7%) were pitting scars and 4 (11.8%) were associated with calcinosis cutis. Out of 50 DUs in hands without ulnar artery stenosis, 30 (60%)

TABLE 4 Disease-related and traditional cardiovascular risk factors in patients with and without UAO

Characteristic	UAO (17 SSc patients)	No UAO (62 SSc patients)	*P*-value
lcSSc:dcSSc	13:4	32:30	0.097
Female sex, *n* (%)	14 (82.4)	56 (90.3)	0.396
Age, mean (S.D.), years	62.1 (12.3)	56.4 (14.4)	0.141
Disease duration, mean (S.D.), months	170 (132.7)	65.8 (73.8)	0.001*
Age at diagnosis, mean (S.D.), years	47.2 (15.4)	50.3 (14.8)	0.452
Mean mRSS (median)	13.4 (11.5)	10.5 (8.5)	0.152
ANA, *n* (%)	17/17 (100)	60/62 (96.8)	1.000
Centromere antibody, *n* (%)	10/17 (58.8)	23/62 (37.1)	0.108
SCL-70 antibody, *n* (%)	2/17 (11.8)	22/62 (35.5)	0.075
Anti-ET_AR antibody (cut-off 10.4), *n* (%)	5/16 (31.3)	26/60 (43.3)	0.568
Anti-AT_1R antibody (cut-off 9.5), *n* (%)	7/16 (43.8)	31/60 (51.7)	0.574
aPL, *n* (%)	2/17 (11.8)	3/62 (4.8)	0.292
BMI, mean (S.D.)	24.8 (6.5)	24.5 (3.3)	0.884
Dyslipidaemia, *n* (%)	9 (52.9)	35 (56.5)	0.796
Cholesterol levels, mean (S.D.), mg/dl	216.8 (56.4)	221.2 (41.6)	0.719
LDL, mean (S.D.), mg/dl	128.9 (36.3)	127.7 (38.1)	0.903
HDL, mean (S.D.), mg/dl	64.2 (24.9)	64.1 (17.5)	0.983
Triglyceride, mean (S.D.), mg/dl	132.5 (107.8)	142.4 (79.1)	0.675
Hypertension, *n* (%)	7 (41.2)	24 (38.7)	0.854
Systolic blood pressure, mean (S.D.), mmHg	124.3 (21.9)	129.3 (22.5)	0.442
Diastolic blood pressure, mean (S.D.), mmHg	74.3 (11.5)	75.5 (11.4)	0.725
Smoking (current or former), *n* (%)	10/17 (58.8)	30/62 (48.4)	0.446
Nicotine use, pack-years	18.3 (31.3)	9.4 (14.5)	0.340
Diabetes, *n* (%)	1 (5.9)	2 (3.2)	0.522
Coronary heart disease, *n* (%)	3 (17.6)	7 (11.3)	0.441
Perpiheral arterial vessel disease, *n* (%)	2 (11.8)	1 (1.6)	0.115
RP, *n* (%)	17 (100)	56 (90.3)	0.331

*Statistically significant after Bonferroni correction.

were fingertip ulcers, 10 (20%) were pitting scars, 7 (14%) were located over the MCP, PIP or DIP joints and 3 (6%) were associated with calcinosis cutis.

Association of anti-ET_AR and anti-AT_1R autoantibodies with UAO

The frequency of antibodies against ET_AR and AT_1R is shown in Table 1. Both antibody specificities were detected in 26 patients, and anti-ET_AR and anti-AT_1R autoantibody levels were highly correlated with each other ($r = 0.911$, $P < 0.001$). There was no significant difference in anti-AT_1R and anti-ET_AR antibody levels in patients with or without UAO (10.7 ± 8.4 *vs* 11.3 ± 7.9 anti-AT_1R antibody units, $P = 0.802$; 10.6 ± 8.7 *vs* 11.9 ± 8.2 anti-ET_AR units, $P = 0.601$, respectively). The area under the receiver operating characteristic curve for anti-ET_AR and anti-AT_1R antibody levels predictive for UAOs at baseline was 0.42 (95% CI 0.26, 0.48) and 0.47 (95% CI 0.31, 0.62), respectively.

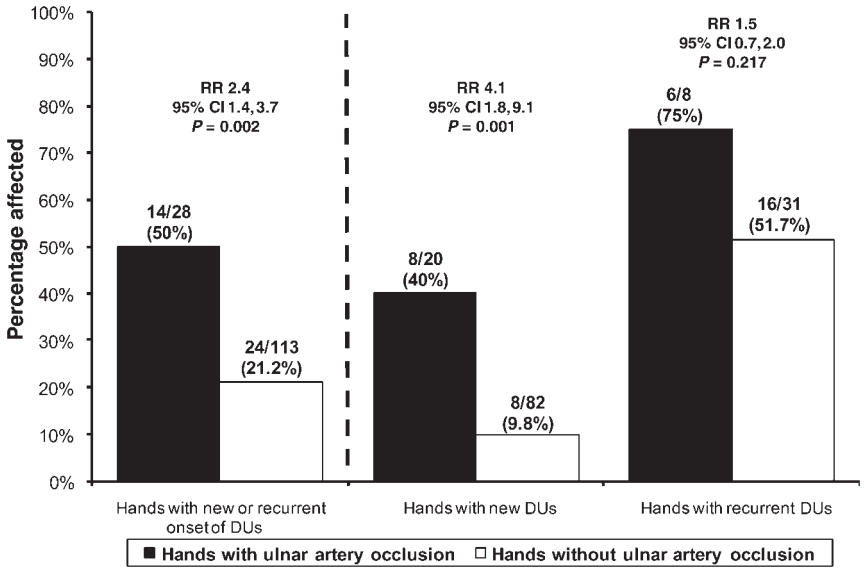
Discussion

DUs are frequent [23] and have a major impact on the quality of life in patients with SSc [24, 25]. Several factors have been associated with DU in previous studies, such as diffuse subtype, male gender, longer disease duration, pulmonary hypertension, high inflammation parameters, early onset of RP, pathological capillaroscopy findings and a higher mRSS [26, 27]. The present study suggests that UAO is an additional predictive factor of DU in scleroderma. We detected a high frequency of UAO in an unselected patient cohort with diffuse and limited scleroderma by CDS. Longer disease duration was the only factor associated with the presence of UAO in our study. However, UAO is not restricted to patients with late-stage disease.

Various studies referred the utility of CDS in differentiation between primary and secondary RP [28–33]. Unfortunately, most studies did not specify results for different CTDs. Hand and finger artery involvement, especially in SSc patients, was reported in only a few studies and case reports using CDS [1, 3–5].

Stafford *et al.* [1] observed a smooth thickening of the ulnar arterial wall in 10/19 SSc patients (in one patient a calcified ulnar artery), in contrast to that of the radial artery in only 2/20 SSc patients. Moreover, the ulnar artery was significantly narrowed compared with 20 matched controls. Consistent with our findings, these changes were found in both SSc subtypes with a non-significant trend for longer disease duration. Bregenzer *et al.* [3] detected increased resistive indices of the distal palmar arteries in SSc, consistent with our findings. Schmidt *et al.* [4]

FIG. 1 Onset of new or recurrent DUs during follow-up (mean 53 months) in upper extremities with and without UAO.



described a small ulnar artery lumen with reduced pulsation and thickened, slightly hyperechoic artery walls in SSc patients using CDS. These findings can be confirmed by our study. In a second CDS study, Schmidt *et al.* [32] reported on 14 ulnar but no radial artery occlusions in 135 patients with suspected RP, including 19 patients with SSc. In contrast, in a recent CDS study on 48 patients with secondary RP, including 32 patients with SSc, UAO was not reported [33]. However, patient characteristics of these 32 SSc patients, in particular disease duration, were not given. Recently Rosato *et al.* [5] found macrovascular damage assessed by CDS at the proper palmar digital arteries in 36 SSc patients correlated with longer disease duration.

The advantage of CDS is the ability to see haemodynamic changes by analysing spectral waveform patterns. We found a significant decreased blood flow and higher resistive index in both the radial and ulnar artery in early as well as late scleroderma patients compared with healthy controls. In agreement with our data in SSc patients, Chikui *et al.* [28] found similar haemodynamic changes in patients with primary RP and other connective disease patients, but no UAO was reported. We suggest that the development of UAO may be a distinct feature of SSc vascular disease.

Several studies used convential angiography, digital subtraction angiography (DSA) or magnetic resonance angiography (MRA) for imaging of macrovascular involvement in SSc [2, 6–15, 34, 35]. Ulnar artery stenosis and occlusion have been frequently observed by DSA, whereas the radial artery was rarely affected [2, 6, 7, 9–12]. The association of UAO and DUs was noted in one of these studies [2]. However, the comparison of our data with previous studies may be difficult, since DUs were not subclassified as suggested recently [36]. In two studies, macrovascular damage and vascular occlusion were found to be associated with anti-topo-1 [5, 11]. We were not able to confirm this hypothesis in our study group; in contrast, lcSSc patients tended to have UAO more frequently than dcSSc and anti-topo-1 Ab-positive patients.

An MRA study on 38 SSc patients revealed that 35 (92%) had occlusions of at least one digital artery. Twenty-three (61%) patients had four or more damaged arteries associated with DUs (including pitting scars) [13]. In 2008, in a micro-MRA study on eight SSc patients, Wang *et al.* [14] described an inverse correlation of digital artery lumen and disease duration. One year later they reported a case of improvement in the digital vasculature assessed by micro-MRA in an SSc patient after high-dose immunosuppressive therapy and autologous haematopoietic cell transplantation [34].

In the present study, DSA was performed in only three patients of our cohort; however, in all three cases the CDS findings could be confirmed. The reliability of CDS to assess hand artery occlusions in comparison with DSA and MRA has been demonstrated by several groups [37, 38].

The lack of compensatory increase in blood flow of the radial artery may be one mechanism in the occurrence of new or recurrent DUs in the presence of UAO. We analysed radial artery flow in upper extremities with ipsilateral UAO and examined whether the radial artery flow was increased compared with upper extremities without UAO. In contrast to studies on patients with removal of the radial artery for coronary artery bypass grafting and consecutive increase in ulnar artery blood flow [39–43], we found no compensatory increase of the ipsilateral radial artery flow in upper extremities with UAO. Obviously this may be a consequence of SSc vascular disease process itself, with a defect of endothelial-dependent arterial and

arteriolar relaxation and wall compliance [44]. Accordingly, we found a significantly lower PSV and EDV in the radial and ulnar arteries in our SSc patients compared with controls.

Previously Riemekasten *et al.* [17] reported on the role of functional autoantibodies against vascular receptors in SSc associated with the development of DUs, pulmonary artery hypertension and lung fibrosis. Using the same test system, UAO at baseline was not associated with anti-ET_AR or anti-AT_1R autoantibodies. Patients with and without UAO had antibody concentrations comparable with the levels previously found in SSc in general, yet they were lower than the levels observed in patients with DUs [17]. Because we performed US examination only at baseline, we are not aware of possible development of new UAOs during the follow-up period, and a predictive cut-off needs to be established in larger prospective cohorts. As another limitation of the study we probably missed DUs that occurred after baseline but disappeared between follow-up visits. This may lead to an underestimation of DUs during follow-up.

In summary, our study demonstrates that UAO is frequent and predictive of new DU in SSc patients. CDS is an easy imaging procedure to confirm clinically suspected UAO. Therefore it should be part of routine assessment for SSc patients. Recently regression of ulnar artery stenosis was observed during bosentan treatment in a single SSc patient [35]. Further studies should show whether UAO can be prevented by the use of vasoactive drugs.

Rheumatology key messages

- Blood flow is significantly decreased in radial and ulnar arteries in SSc patients.
- UAO is frequently detectable by CDS in SSc patients.
- UAO is an important risk factor for the development of DUs.

Acknowledgements

The authors would like to thank Dr Müller-Ladner for critical revision of the manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Stafford L, Englert H, Gover J *et al*. Distribution of macrovascular disease in scleroderma. Ann Rheum Dis 1998;57:476–79.

2 Taylor MH, McFadden JA, Bolster MB *et al*. Ulnar artery involvement in systemic sclerosis (scleroderma). J Rheumatol 2002;29:102–6.

3 Bregenzer N, Distler O, Meyringer R *et al*. Doppler ultrasound identifies increased resistive indices in SSc. Ann Rheum Dis 2004;63:109–10.

4 Schmidt WA, Wernicke D, Kiefer E *et al*. Colour duplex sonography of finger arteries in vasculitis and in systemic sclerosis. Ann Rheum Dis 2006;65:265–7.

5 Rosato E, Gigante A, Barbano B *et al*. In systemic sclerosis macrovascular damage of hands digital arteries correlates with microvascular damage. Microvasc Res 2011; 82:410–5.

6 Dabich L, Bookstein JJ, Zweifler A *et al*. Digital arteries in patients with scleroderma. Arteriographic and plethysmographic study. Arch Intern Med 1972;130: 708–14.

7 Janevski B. Arteries of the hand in patients with scleroderma. Diagn Imaging Clin Med 1986;55: 262–5.

8 Youssef P, Englert H, Bertouch J. Large vessel occlusive disease associated with CREST syndrome and scleroderma. Ann Rheum Dis 1993;52:464–6.

9 Stücker M, Quinna S, Memmel U *et al*. Macroangiopathy of the upper extremities in progressive systemic sclerosis. Eur J Med Res 2000;5:295–302.

10 Dick EA, Aviv R, Francis I *et al*. Catheter angiography and angioplasty in patients with scleroderma. Br J Radiol 2001;74:1091–6.

11 Hasegawa M, Nagai Y, Tamura A *et al*. Arteriographic evaluation of vascular changes of the extremities in patients with systemic sclerosis. Br J Dermatol 2006;155: 1159–64.

12 Park JH, Sung Y, Bae S *et al*. Ulnar artery vasculopathy in systemic sclerosis. Rheumatol Int 2009;29:1081–6.

13 Allanore Y, Seror R, Chevrot A *et al*. Hand vascular involvement assessed by magnetic resonance angiography in systemic sclerosis. Arthritis Rheum 2007; 56:2747–54.

14 Wang J, Yarnykh VL, Molitor JA *et al*. Micro magnetic resonance angiography of the finger in systemic sclerosis. Rheumatology 2008;47:1239–43.

15 Sheehan JJ, Fan Z, Davarpanah AH *et al*. Nonenhanced MR angiography of the hand with flow-sensitive dephasing-prepared balanced SSFP sequence: initial experience with systemic sclerosis. Radiology 2011;259: 248–56.

16 Zimmerman NB. Occlusive vascular disorders of the upper extremity. Hand Clin 1993;9:139–50.

17 Riemekasten G, Philippe A, Näther M *et al*. Involvement of functional autoantibodies against vascular receptors in systemic sclerosis. Ann Rheum Dis 2011;70:530–6.

18 Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.

19 LeRoy EC, Black C, Fleischmajer R *et al*. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202–5.

20 LeRoy EC, Medsger TA. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001; 28:1573–6.

21 Lowering blood cholesterol to prevent heart disease. NIH Consens Statement 1985;5:27. http://www.ncbi.nlm.nih

.gov/pubmed/3887139 (14 December 2011, date last accessed).

22 Triglyceride, high density lipoprotein, and coronary heart disease. NIH Consens Statement 1992;10:1–28, http://www.ncbi.nlm.nih.gov/pubmed/1286136 (14 December 2011, date last accessed).

23 Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. Autoimmun Rev 2006;5:125–28.

24 Zelenietz C, Pope J. Differences in disability as measured by the Health Assessment Questionnaire between patients with and without digital ulcers in systemic sclerosis: a post hoc analysis of pooled data from two randomised controlled trials in digital ulcers using bosentan. Ann Rheum Dis 2010;69:2055–56.

25 Mouthon L, Mestre-Stanislas C, Bérezné A *et al*. Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. Ann Rheum Dis 2010;69: 214–7.

26 Hanitsch LG, Burmester G, Witt C *et al*. Skin sclerosis is only of limited value to identify SSc patients with severe manifestations–an analysis of a distinct patient subgroup of the German Systemic Sclerosis Network (DNSS) Register. Rheumatology 2009;48:70–3.

27 Sunderkötter C, Herrgott I, Brückner C *et al*. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. Br J Dermatol 2009;160:835–43.

28 Chikui T, Izumi M, Eguchi K *et al*. Doppler spectral waveform analysis of arteries of the hand in patients with Raynaud's phenomenon as compared with healthy subjects. AJR Am J Roentgenol 1999;172:1605–09.

29 Keberle M, Tony HP, Jahns R *et al*. Assessment of microvascular changes in Raynaud's phenomenon and connective tissue disease using colour doppler ultrasound. Rheumatology 2000;39:1206–13.

30 Lee SI, Lee SY, Yoo WH. The usefulness of power Doppler ultrasonography in differentiating primary and secondary Raynaud's phenomenon. Clin Rheumatol 2006;25:814–8.

31 Kim S, Kim H, Jeong Y *et al*. The diagnostic accuracy of power Doppler ultrasonography for differentiating secondary from primary Raynaud's phenomenon in undifferentiated connective tissue disease. Clin Rheumatol 2008; 27:783–6.

32 Schmidt WA, Krause A, Schicke B *et al*. Color Doppler ultrasonography of hand and finger arteries to differentiate primary from secondary forms of Raynaud's phenomenon. J Rheumatol 2008;35:1591–8.

33 Toprak U, Hayretci M, Erhuner Z *et al*. Dynamic Doppler evaluation of the hand arteries to distinguish between primary and secondary Raynaud phenomenon. AJR Am J Roentgenol 2011;197:W175–80.

34 Wang J, Nash RA, Chu B *et al*. Improvements in digital vasculature observed using micro magnetic resonance angiography after high-dose immunosuppression for severe systemic sclerosis. Bone Marrow Transpl 2009;44: 387–9.

35 Ichimura Y, Asano Y, Hatano M *et al*. Significant attenuation of macrovascular involvement by bosentan in a patient with diffuse cutaneous systemic sclerosis with multiple digital ulcers and gangrene. Modern rheumatology / the Japan Rheumatism Association 2011; 21:548–52.

36 Amanzi L, Braschi F, Fiori G *et al*. Digital ulcers in scleroderma: staging, characteristics and sub-setting through observation of 1614 digital lesions. Rheumatology 2010; 49:1374–82.

37 Langholz J, Ladleif M, Blank B *et al*. Colour coded duplex sonography in ischemic finger artery disease–a comparison with hand arteriography. VASA 1997;26:85–90.

38 Winterer JT, Ennker J, Scheffler K *et al*. Gadolinium-enhanced elliptically reordered three-dimensional MR angiography in the assessment of hand vascularization before radial artery harvest for coronary artery bypass grafting: first experience. Invest Radiol 2001;36:501–8.

39 Lohr JM, Paget DS, Smith JM *et al*. Upper extremity hemodynamic changes after radial artery harvest for coronary artery bypass grafting. Ann Vasc Surg 2000;14: 56–62.

40 Brodman RF, Hirsh LE, Frame R. Effect of radial artery harvest on collateral forearm blood flow and digital perfusion. J Thorac Cardiovasc Surg 2002;123:512–6.

41 Gaudino M, Serricchio M, Tondi P *et al*. Chronic compensatory increase in ulnar flow and accelerated atherosclerosis after radial artery removal for coronary artery bypass. J Thorac Cardiovasc Surg 2005;130:9–12.

42 Gaudino M, Glieca F, Luciani N *et al*. Ten-year echo-Doppler evaluation of forearm circulation following radial artery removal for coronary artery bypass grafting. Eur J Cardiothorac Surg 2006;29:71–3.

43 Gaudino M, Anselmi A, Serricchio M *et al*. Late haemodynamic and functional consequences of radial artery removal on the forearm circulation. Int J Cardiol 2008;129: 255–8.

44 La Civita L, Rossi M, Vagheggini G *et al*. Microvascular involvement in systemic sclerosis: laser Doppler evaluation of reactivity to acetylcholine and sodium nitroprusside by iontophoresis. Ann Rheum Dis 1998;57:52–5.