

The Renal Resistive Index: A New Biomarker for the Follow-up of Vascular Modifications in Systemic Sclerosis

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ABSTRACT. Objective. The aim of the present retrospective observational study was to evaluate the change of Renal Resistive Index (RRI) over time (Δ RRI) and under treatment in patients with systemic sclerosis (SSc) as well as to correlate these changes with disease complications.

Methods. Two hundred thirty patients [29 male, median age 57 (IQR 48–67) yrs] were enrolled. At baseline and follow-up (3.43, IQR 2.81–4.45 yrs), we collected the following data: disease variables, nailfold video-capillaroscopy (NVC) pattern, forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (DLCO), systolic pulmonary arterial pressure (sPAP), presence of interstitial lung disease, RRI, evaluation of glomerular filtration rate, and new onset of pulmonary arterial hypertension (PAH).

Results. RRI value is high in SSc patients with digital ulcers and anticentromere antibodies, active and late NVC patterns, and limited cutaneous SSc. A significant correlation was observed between Δ RRI and Δ sPAP ($R = 0.17$, $P = 0.02$), with statistically higher Δ RRI (0.08 ± 0.02 vs 0.03 ± 0.05 , $P = 0.04$) in patients complicated by PAH onset. No other new-onset complication was associated with Δ RRI. The receiver-operating characteristic curve analysis confirmed the predictive role of Δ RRI in development of new PAH (area under the curve 0.84, 95% CI 0.75–0.93, $P = 0.02$). In patients with SSc never exposed to sildenafil, Δ RRI was higher (0.04 ± 0.05) compared to both patients exposed to sildenafil during the study period (0.01 ± 0.05 , $P = 0.03$) or in those exposed at the time of baseline evaluation (0.00 ± 0.05 , $P = 0.01$).

Conclusion. RRI and its variation in time are a reliable marker of SSc-related vasculopathy, both in renal and extrarenal compartments.

Key Indexing Terms: renal Doppler ultrasonography, renal resistive index, systemic sclerosis, vasculopathy

Systemic sclerosis (SSc) is an autoimmune disease characterized by a complex pathogenesis¹. The disease affects the vascular system widely in the body, in particular the microcirculation of the fingers, lung, heart, and kidney. In SSc, the kidney is frequently involved, and renal manifestations range from reduction of glomerular filtrate rate (GFR), abnormal urinalysis, reduced renal functional reserve, antiphospholipid-associated

nephropathy, myeloperoxidase-antineutrophil cytoplasmic antibody-associated glomerulonephritis and vasculitis, and a peculiar acute condition known as scleroderma renal crisis (SRC). Among renal manifestations, SSc-associated vasculopathy is characterized by abnormal renal vascular resistance indices and endothelial markers². In SSc, the microcirculation of the kidney may be investigated with renal Doppler ultrasonography (RDU)³ and the renal resistive index (RRI), which is a noninvasive tool widely used in physiological and pathological conditions⁴. This technique allows a spectrum analysis of the arcuate arteries in the region of the corticomedullary junction and the interlobar arteries along the border of medullary pyramids. The increase of renal vascular resistance in renal artery stenosis (RAS), using RRI as a measure of functional changes to structural vasculature, has been previously described⁵. In fact, RRI can detect modifications of the vascular distensibility, compliance, and resistance due to pathologic mechanisms. In SSc, RRI is significantly increased and correlates with fibrotic and vascular features that are mainly the basis for the development of SRC⁶, digital ulcers (DU)⁷, and capillaroscopic modifications⁸. Since glomeruli account for 8% of the renal parenchymal thickness and the highest percentage is occupied by vascular and tubulo-interstitial components, RRI tends to be more sensitive to vascular lesions than glomerulonephritis⁹.

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In fact, in several studies, RRI correlates with pathologic lesions such as arteriolosclerosis, glomerulosclerosis, tubulo-interstitial damage, and vascular lesions^{10,11}. An SSc autopsy case-control study found a significantly higher number of abnormalities in the small arteries of SSc patients than healthy controls. Although the most renal vascular structural changes were found in patients with SRC, the authors showed a significant increase in absolute intimal area and luminal occlusion in all vessels in SSc patients with or without SRC¹². RRI increased with age, and in several conditions (e.g., arterial hypertension and renal arterial stenosis), a value of RRI > 0.70 is considered pathological. In our previous study, we showed that a cutoff of RRI > 0.68 is predictive of mortality (sensitivity 88.5%, specificity 50.9%). We can assume that RRI values ≥ 0.68 and ≤ 0.70 are moderately high, and values > 0.70 are high^{7,13}.

In SSc patients with normal renal function and blood pressure, a subclinical renal vascular disease has been demonstrated¹⁴. In fact, vascular abnormalities were detected in renal pathological specimens obtained from non-SRC patients with a 3-year follow-up¹⁵. This evidence clearly demonstrates that SSc renal involvement is often subclinical and tightly related to vascular injury and consequent chronic hypoxia, which usually has a better prognosis than SRC¹⁶.

The aim of the present retrospective observational study was to evaluate in patients with SSc the change of RRI over time (Δ RRI) and under treatment, as well as to correlate these changes with disease complications.

MATERIALS AND METHODS

Study population. Patients affected by SSc, classified according to American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for SSc¹⁷ and undergoing 2 RRI determinations on RDU since SSc diagnosis were retrospectively enrolled in the study. Patients were categorized as very early diagnosis of systemic sclerosis (VEDOSS) if they were fulfilling the ACR/EULAR 2013 criteria only with the presence of the diagnostic VEDOSS criteria¹⁸; otherwise, they were classified as established SSc. Subsets of SSc cutaneous involvement were defined according to LeRoy, *et al*¹⁹.

Patients with renal failure, SRC, RAS, glomerulonephritis, pulmonary disease unrelated to SSc, and cardiac failure were excluded, as well as pregnant or breastfeeding women. The study complies with the Declaration of Helsinki. The local ethical committee approved the research protocol (CEAVC 12350_oss), and informed consent was obtained from all patients. **Data collection.** At baseline and follow-up, clinical, instrumental, and functional data were collected. The following variables were obtained: age, disease duration [from first non-Raynaud phenomenon (RP) symptom], presence of telangiectasias, presence of dyspnea, presence/history of DU²⁰, modified Rodnan skin score (mRSS)²¹, gastrointestinal and joint involvement as clinical features, nailfold videocapillaroscopy (NVC) pattern²², forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (DLCO) corrected for hemoglobin concentration²³, systolic pulmonary arterial pressure (sPAP) on transthoracic echocardiography²⁴, presence of interstitial lung disease (ILD) at high-resolution computerized tomography, history of pulmonary arterial hypertension (PAH; according to international guidelines)²⁵, RRI on RDU⁶ as instrumental data, evaluation of glomerular filtration rate (eGFR)²⁶, and autoantibody positivity as laboratory data. During follow-up, new-onset telangiectasias, DU, PAH, ILD, dyspnea, and SRC were also recorded.

Statistical analysis. All results are expressed as mean \pm SD or median

and IQR, as appropriate. SPSS version 25.0 software was used for the statistical analysis. The coefficient of kurtosis was used to evaluate normal distribution of data. A multivariate analysis was applied for the estimation of the relationship of RRI with the clinical features. A receiver-operating characteristic (ROC) curve analysis was performed to analyze the prognostic accuracy of RRI toward development of outcomes in the follow-up. All time-to-event endpoints were estimated with the Kaplan-Meier method and analyzed with the log-rank test. HR with 95% CI were calculated with the use of Cox regression models. Group comparisons were made by unpaired 2-tailed *t*-test or Mann-Whitney test, as appropriate. Pearson product-moment correlation coefficient or Spearman rank correlation coefficient, as appropriate, were used to test for an association between numerical variables. The chi-square test or Fisher exact test, as appropriate, was used to compare categorical variables. *P* values < 0.05 were considered significant.

RESULTS

Two hundred and thirty patients [29 male, median age 57 (48–67) yrs] were enrolled in the protocol. Thirty satisfied the ACR/EULAR 2013 criteria with VEDOSS features only, while 200 presented with established SSc; 65 (28.3%) had diffuse (dcSSc), 132 (57.4%) limited SSc (lcSSc), and 33 (14.3%) a sine scleroderma subset. In Table 1, the baseline clinical features of patients with SSc are shown. The median value of eGFR was 97.50 mL/min/1.73 m² (80.21–118.75), and median value of RRI was 0.68 \pm 0.07. In anticentromere antibody (ACA)-positive SSc patients, the RRI values were higher than in patients characterized by the presence of other autoantibodies (0.70 \pm 0.06 vs 0.68 \pm 0.07, *P* = 0.010). In SSc patients with DU, the mean RRI value was significantly higher compared to SSc patients without DU (0.70 \pm 0.06 vs 0.68 \pm 0.07, *P* = 0.011). The VEDOSS patients did not show any difference in RRI values compared to those affected by an overt disease (0.68 \pm 0.06 vs 0.69 \pm 0.07, *P* = 0.743). Meanwhile, the RRI value was significantly (*P* = 0.010) higher in lcSSc (0.70 \pm 0.07) than sine scleroderma (0.67 \pm 0.06) and dcSSc (0.68 \pm 0.07). No significant difference of RRI value was observed between sine scleroderma and dcSSc. Patients with active and late NVC patterns showed RRI values significantly higher than SSc patients with nonspecific and early patterns (0.67 \pm 0.07 vs 0.69 \pm 0.06, *P* = 0.031).

In Table 2, the changes (Δ) of SSc features during a median follow-up of 3.4 (2.8–4.4) years are shown. No significant correlation was observed between Δ RRI and Δ mRSS (*R* = 0.112, *P* = 0.119) or Δ FVC (*R* = 0.026, *P* = 0.712) or Δ DLCO (*R* = -0.091, *P* = 0.189) or Δ eGFR (*R* = -0.106, *P* = 0.133). Conversely, a significant correlation was observed between Δ RRI and Δ sPAP (*R* = 0.173, *P* = 0.023), with statistically higher Δ RRI (0.08 \pm 0.02 vs 0.03 \pm 0.05, *P* = 0.038) in patients complicated by PAH onset (Table 3). Five (2.2%) patients with SSc had new-onset SRC. No significant differences of Δ RRI was observed between SSc patients with or without new-onset SRC (0.04 \pm 0.06 vs 0.03 \pm 0.05, *P* = 0.535). No other new-onset complication was associated with Δ RRI (Table 3).

At univariate regression analysis, Δ RRI (HR 7.127, 95% CI 0.996–9.101, *P* = 0.05), Δ sPAP (HR 1.082, 95% CI 1.038–1.128, *P* < 0.001), and disease duration (HR 1.077, 95% CI 1.006–1.154, *P* = 0.034) were predictive of new-onset PAH, although only Δ sPAP was independently associated with

Table 1. Demographic and clinical features of systemic sclerosis patients at baseline.

	Values
Age, yrs, median (IQR)	57 (48–67)
Male sex, n (%)	29 (12.6)
Smoke exposure, n (%)	30 (13.0)
Time from RP onset, yrs, median (IQR)	10 (4–20)
Time from disease onset, yrs, median (IQR)	6 (2–11)
VEDOSS patients, n (%)	30 (13.0)
Cutaneous subset: sine scleroderma/ limited/diffuse	33 (14.3)/ 132 (57.4)/65 (28.3)
mRSS, median (IQR)	5 (0–11)
Digital ulcer history/presence, n (%)	88 (38.3)
Late NVC pattern, n (%)	64 (27.8)
PAH, n (%)	13 (5.7)
sPAP, median (IQR)	27 (23–31)
Telangiectasias, n (%)	52 (22.6)
ILD, n (%)	63 (27.4)
Dyspnea, n (%)	71 (30.9)
%FVC, mean (SD)	102 (21)
%DLCO, mean (SD)	74 (18)
Upper GI symptoms, n (%)	152 (66.1)
Lower GI symptoms, n (%)	28 (12.2)
Arthritis, n (%)	32 (13.9)
Tendon friction rubs, n (%)	18 (7.8)
History of SRC, n (%)	2 (0.9)
Increase of CRP, n (%)	22 (9.6)
Increase of ESR, n (%)	58 (25.5)
ACA positivity, n (%)	117 (50.9)
Scl70 positivity, n (%)	81 (35.2)
RNA polymerase III positivity, n (%)	13 (5.7)
eGFR, median (IQR)	97.50 (80.21–118.75)
RRI, mean (SD)	0.68 (0.07)

ACA: anticentromere antibody; CRP: C-reactive protein; DLCO: diffusing lung capacity for carbon monoxide; DU: digital ulcer; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; ILD: interstitial lung disease; GI: gastrointestinal; mRSS: modified Rodnan skin score; NVC: nailfold videocapillaroscopy; PAH: pulmonary arterial hypertension; sPAP: systolic pulmonary arterial pressure; RP: Raynaud phenomenon; RRI: renal resistive index; SRC: scleroderma renal crisis; VEDOSS: very early diagnosis of systemic sclerosis.

new PAH onset (HR 1.076, 95% CI 1.022–1.134, $P = 0.006$) at multivariate analysis. The ROC curve analysis confirmed the predictive role of Δ RRI in development of new PAH (area under the curve 0.841, 95% CI 0.753–0.930, $P = 0.019$; Figure 1). Interestingly, a significant difference of Δ eGFR was also observed between SSc patients with PAH and without PAH (-22.4 ± 25.5 vs -8.4 ± 17.9 mL/min/1.73 m², $P = 0.026$).

In Table 4, the pharmacological treatments are reported at baseline and follow-up, while the Δ RRI in different classes of drug therapies are shown in Table 5. In patients with SSc never exposed to sildenafil, Δ RRI was higher (0.03 ± 0.05) compared to patients exposed to sildenafil during the study period (0.01 ± 0.05 , $P = 0.028$) or in those exposed at the time of baseline evaluation (0.00 ± 0.05 , $P = 0.009$). No significant Δ RRI differences were observed when compared to patients with SSc newly treated during follow-up (0.02 ± 0.05 , $P = 0.582$).

Table 2. Changes of features of SSc disease at follow-up.

	Values
Change in mRSS, mean (SD)	+0.62 (3.98)
New onset of DU, n (%)	16 (7.0)
Worsening of NVC pattern, n (%)	25 (10.9)
New onset of PAH, n (%)	4 (1.7)
Change in sPAP, mean (SD)	1.24 (9.15)
New onset of telangiectasias, n (%)	10 (4.3)
New onset of ILD, n (%)	10 (4.3)
New onset of dyspnea, n (%)	35 (15.2)
Change in %FVC, mean (SD)	-1.50 (15.09)
Change in %DLCO, mean (SD)	-6.32 (13.33)
New onset of SRC, n (%)	5 (2.2)
Change in eGFR, mean (SD)	-9.36 (18.58)
Change in RRI, mean (SD)	0.02 (0.05)

CRP: C-reactive protein; DLCO: diffusing lung capacity for carbon monoxide; DU: digital ulcer; eGFR: estimated glomerular filtration rate; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; ILD: interstitial lung disease; mRSS: modified Rodnan skin score; PAH: pulmonary arterial hypertension; RRI: renal resistive index; sPAP: systolic pulmonary arterial pressure; SRC: scleroderma renal crisis; NVC: nailfold videocapillaroscopy.

Table 3. Change of RRI and new onset of disease complication.

	Δ RRI		P
	Yes	No	
New onset of DU, n (%)	0.05 \pm 0.06	0.02 \pm 0.05	0.059
Worsening of NVC pattern, n (%)	0.04 \pm 0.04	0.03 \pm 0.05	0.707
New onset of PAH, n (%)	0.08 \pm 0.02	0.03 \pm 0.05	0.038*
New onset of telangiectasias, n (%)	0.02 \pm 0.05	0.03 \pm 0.05	0.307
New onset of ILD, n (%)	0.04 \pm 0.04	0.03 \pm 0.05	0.512
New onset of dyspnea, n (%)	0.03 \pm 0.06	0.02 \pm 0.05	0.423
New onset of SRC, n (%)	0.04 \pm 0.06	0.03 \pm 0.05	0.535

Values in bold are statistically significant. DU: digital ulcer; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; SRC: scleroderma renal crisis; NVC: nailfold videocapillaroscopy; Δ RRI: change in Renal Resistive Index.

Conversely, Δ RRI was lower in patients not exposed to calcium channel blockers (CCB) during the study period (0.02 ± 0.04) compared to those treated with CCB during the study (0.03 ± 0.05 , $P = 0.027$) or exposed to CCB at baseline (0.03 ± 0.06 , $P = 0.033$). No significant differences of Δ RRI were observed between patients with SSc newly treated during follow-up and patients with SSc treated during the study period (0.03 ± 0.04 vs 0.03 ± 0.05 , $P = 0.477$). In patients with SSc treated with iloprost at some point during the study period, Δ RRI was higher than in untreated patients (0.03 ± 0.05 vs 0.02 ± 0.05 , $P = 0.033$). No significant differences of Δ RRI were observed in SSc patients treated with iloprost at baseline or newly treated during follow-up, as was also observed with the other vasodilative and vasoactive drugs listed in Table 5.

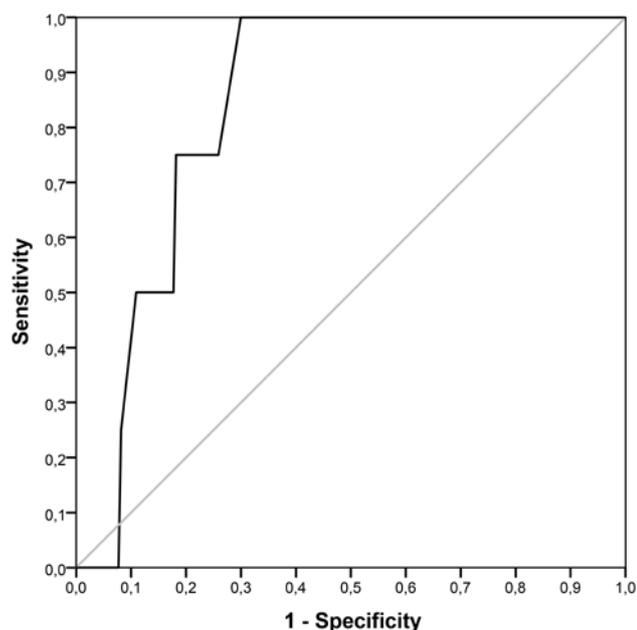


Figure 1. ROC curve for Δ RRI as predictor of new-onset PAH. PAH: pulmonary arterial hypertension; ROC: receiver-operating characteristic; Δ RRI: change in Renal Resistive Index.

DISCUSSION

Our data clearly show that the Δ RRI changed progressively during the 3.4 years of follow-up. Moreover, it correlated with Δ sPAP and was significantly higher in patients with new-onset PAH. In SSc, PAH is a severe vascular complication most commonly occurring in limited cutaneous ACA-positive patients²⁷. In our population, ACA-positive/limited cutaneous patients showed a higher RRI than ACA-negative and diffuse cutaneous subset or sine scleroderma patients. Similarly, patients with DU showed a higher RRI than patients without DU, confirming RRI as a reliable marker of new DU occurrence⁶.

Although several manifestations of renal involvement are described, SRC remains one of the most feared complications

of SSc. It was the most severe complication in SSc and the most frequent cause of death in these patients. It is characterized by episodic renal vasospasm and proliferative obliterative vasculopathy with acute onset of moderate-to-severe hypertension and oliguric renal failure². Asymptomatic increased renal stiffness is reported in several studies, showing an inverse correlation with GFR. In addition, increase of RRI may predict the occurrence of new DU, increasing with capillaroscopic damage^{6,7,8}.

These associations reflect the link between RRI and vascular involvement in different organs during the disease course. In fact, fibrotic intimal hyperplasia, endothelial dysfunction, and occlusive vasculopathy are common features of RP, DU, SRC, and PAH²⁸. For this reason, it could be hypothesized that the increased RRI may represent a clinical biomarker of renal vascular injury. As far as we know, no studies focusing on PAH, RRI, and renal function have been performed in patients with SSc. In our population, PAH patients showed over time a reduction of GFR and an increase of Δ RRI. In an observational study on 179 patients with PAH mainly affected by idiopathic PAH, in a follow-up of almost 3 years, our data were confirmed with a GFR mean reduction of 0.85 mL/min/1.73 m² per year. This suggests that the right heart failure might induce further renal hypoperfusion with congestion, thus promoting renal injury and eGFR decrease²⁹. However, several studies have also shown that cardiac output and/or right atrial pressures are hemodynamic variables that are related to eGFR reduction in various pulmonary hypertension groups. Consequently, the renal failure was associated with a higher mortality in patients with PAH³⁰. Further, other factors (venous congestion, inflammatory endothelial dysfunction, vasoconstrictive state, endothelin-1, interleukin-6, angiotensin, and other molecules) can be involved in renal worsening correlated to PAH³⁰. Since PAH is a hemodynamic disease, chronic alterations of pulmonary perfusion can contribute to the reduction of the renal perfusion with slow GFR decline and increased intrarenal stiffness. The VEDOSS patients did not show any difference in RRI values when compared to those affected by an overt disease.

Table 4. Drug therapy in patients with SSc.

	Treated During the Study Period	Treated at Baseline	Newly Treated During Follow-up	Never Treated
Sildenafil, n (%)	52 (22.6)	27 (11.7)	25 (10.9)	174 (75.7)
Bosentan, n (%)	85 (35.7)	64 (27.8)	21 (9.1)	143 (62.2)
Calcium channel blockers, n (%)	131 (56.5)	113 (49.1)	18 (7.8)	96 (41.7)
Statins, n (%)	45 (19.1)	22 (9.6)	23 (10.0)	181 (78.7)
Iloprost, n (%)	99 (42.6)	94 (40.9)	5 (2.2)	128 (55.7)
PGE, n (%)	49 (20.9)	37 (16.1)	12 (5.2)	177 (77.0)
Steroids, n (%)	58 (23.9)	49 (21.3)	9 (3.9)	171 (74.3)
ARB, n (%)	41 (17.8)	26 (11.3)	15 (6.5)	185 (80.4)
Beta blockers, n (%)	16 (7.0)	4 (1.7)	12 (5.2)	209 (90.9)
ACEi, n (%)	48 (20.9)	33 (14.3)	15 (6.5)	177 (77.0)
Immunosuppressants, n (%)	54 (23.5)	32 (13.9)	22 (9.6)	171 (74.3)

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; Δ RRI: change in Renal Resistive Index.

Table 5. Effect of drugs on Δ RRI over the follow-up period.

	Δ RRI				P^{\dagger}		
	Treated During the Study Period	Treated at Baseline	Newly Treated During Follow-up	Never Treated	Ever vs Never	Baseline vs Never	Newly vs Ever
Sildenafil	0.01 ± 0.05	0.00 ± 0.05	0.02 ± 0.058	0.03 ± 0.05	0.028	0.009	0.582
Bosentan	0.02 ± 0.06	0.03 ± 0.05	0.01 ± 0.06	0.03 ± 0.05	0.681	0.664	0.090
Calcium channel blockers	0.03 ± 0.05	0.03 ± 0.06	0.03 ± 0.04	0.02 ± 0.04	0.027	0.033	0.477
Statins	0.03 ± 0.05	0.03 ± 0.04	0.03 ± 0.06	0.03 ± 0.05	0.877	0.753	0.983
Iloprost	0.03 ± 0.05	0.03 ± 0.05	0.06 ± 0.06	0.02 ± 0.05	0.033	0.088	0.084
Alprostadil	0.02 ± 0.05	0.02 ± 0.05	0.03 ± 0.06	0.03 ± 0.05	0.202	0.189	0.845
Steroids	0.03 ± 0.06	0.02 ± 0.06	0.03 ± 0.05	0.03 ± 0.05	0.797	0.617	0.858
ARB	0.02 ± 0.05	0.02 ± 0.05	0.02 ± 0.07	0.03 ± 0.05	0.416	0.698	0.418
Beta blockers	0.03 ± 0.06	0.02 ± 0.06	0.03 ± 0.07	0.03 ± 0.06	0.896	0.775	0.952
ACEi	0.02 ± 0.06	0.02 ± 0.05	0.01 ± 0.05	0.03 ± 0.05	0.527	0.824	0.165
Immunosuppressants	0.02 ± 0.06	0.02 ± 0.06	0.02 ± 0.06	0.06 ± 0.05	0.117	0.148	0.275

Values in bold are statistically significant. † P value from t test. ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; Δ RRI: change in Renal Resistive Index.

Since RRI is increased for renal vasospasm such as in RP and proliferative obliterative vasculopathy, we can presume that renal vascular damage is present also in very early stages of disease for renal vasospasm.

In our study, 36.5% and 3.5% of patients were diagnosed at baseline with systemic hypertension and diabetes, respectively. Although RRI is high in hypertensive and diabetic patients, in our study population, eGFR median was 97.50 (IQR 80.21–118.75) mL/min/1.73 m². It is well known that systemic hypertension and diabetes are comorbidities that lead to chronic kidney failure due to arterial stiffness, which is associated with eGFR reduction³¹. In diabetes, the rapid increase of RRI is negatively correlated with eGFR. In our study, Δ RRI changes were more evident in SSc patients with a nonpathological value of RRI than with a pathological RRI at baseline. It may be hypothesized that SSc renal vasculopathy may determine an independent chronic and slow process increasing intrarenal resistances, as previously suggested¹³.

A reduction of RRI has been previously demonstrated in the interlobar and cortical arteries after iloprost infusion with improvement of the renal blood flow. This evidence suggested that a stable prostacyclin analog might be useful for treatment of SSc renal vasospasm³². At baseline and during follow-up, patients with SSc were treated with several drug classes. However, Δ RRI increased significantly in patients treated with CCB or iloprost, compared to patients who did not receive these drugs. On the contrary, patients exposed to sildenafil showed a significantly lower Δ RRI increase over time in comparison to patients nonexposed to sildenafil.

Our study confirms that RRI and its variation in time are a reliable marker of SSc renal vasculopathy and other extrarenal compartments. To our knowledge, our study is the first to demonstrate that a change in RRI was associated with NVC damage progression and new-onset PAH. In addition, significant changes in RRI are present in patients with SSc treated with vasodilators and, in particular, those treated with sildenafil.

In conclusion, RRI might become not only a useful tool in practice for patients' renal follow-up but also a promising

outcome measure for SSc related vasculopathy. The RRI utility should be confirmed in prospective studies and in randomized clinical trials.

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