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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 (ΔRRI) 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 ΔRRI and ΔsPAP (R = 0.17, $P = 0.02$), with statistically higher ΔRRI (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 ΔRRI. The receiver-operating characteristic curve analysis confirmed the predictive role of ΔRRI 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, ΔRRI 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 pathogenesis[1]. 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 markers[2]. 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 conditions[4]. 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 described[5]. 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 SRC[6], digital ulcers (DU)[7], and capillaroscopic modifications[8]. 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 glomerulonephritis[9].

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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 SRC[12]. 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 demonstrated[14]. In fact, vascular abnormalities were detected in renal pathological specimens obtained from non-SRC patients with a 3-year follow-up[15]. 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 SRC[16].

The aim of the present retrospective observational study was to evaluate in patients with SSc the change of RRI over time (ΔRRI) 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 SSc[17] 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 criteria[18]; 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 DU[20], modified Rodnan skin score (mRSS) [21], gastrointestinal and joint involvement as clinical features, nailfold videocapillaroscopy (NVC) pattern[22], forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (DLCO) corrected for hemoglobin concentration[23], systolic pulmonary arterial pressure (sPAP) on transthoracic echocardiography[24], presence of interstitial lung disease (ILD) at high-resolution computerized tomography, history of pulmonary arterial hypertension (PAH; according to international guidelines) [25], RRI on RDU[6] 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 ± 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 m^2 (80.21–118.75), and median value of RRI was 0.68 ± 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 ± 0.06 vs 0.68 ± 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 ± 0.06 vs 0.68 ± 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 ± 0.06 vs 0.69 ± 0.07, $P = 0.743$). Meanwhile, the RRI value was significantly ($P = 0.010$) higher in lcSSc (0.70 ± 0.07) than sine scleroderma (0.67 ± 0.06) and dcSSc (0.68 ± 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 ± 0.07 vs 0.69 ± 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 ΔRRI and ΔmRSS (R = 0.112, $P = 0.119$) or ΔFVC (R = 0.026, $P = 0.712$) or ΔDLCO (R = –0.091, $P = 0.189$) or ΔeGFR (R = –0.106, $P = 0.133$). Conversely, a significant correlation was observed between ΔRRI and ΔsPAP (R = 0.173, $P = 0.023$), with statistically higher ΔRRI (0.08 ± 0.02 vs 0.03 ± 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 ΔRRI was observed between SSc patients with or without new-onset SRC (0.04 ± 0.06 vs 0.03 ± 0.05, $P = 0.535$). No other new-onset complication was associated with ΔRRI (Table 3).

At univariate regression analysis, ΔRRI (HR 7.127, 95% CI 0.996–9.101, $P = 0.05$), ΔsPAP (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 ΔsPAP 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 ΔRRI 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 ΔeGFR was also observed between SSc patients with PAH and without PAH (−22.4 ± 25.5 vs −8.4 ± 17.9 mL/min/1.73 m^2, $P = 0.026$).

In Table 4, the pharmacological treatments are reported at baseline and follow-up, while the ΔRRI in different classes of drug therapies are shown in Table 5. In patients with SSc never exposed to sildenafil, ΔRRI 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 ΔRRI 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.

	ΔRRI		
	Yes	No	*P*
New onset of DU, n (%)	0.05 ± 0.06	0.02 ± 0.05	0.059
Worsening of NVC pattern, n (%)	0.04 ± 0.04	0.03 ± 0.05	0.707
New onset of PAH, n (%)	0.08 ± 0.02	0.03 ± 0.05	**0.038***
New onset of telangiectasias, n (%)	0.02 ± 0.05	0.03 ± 0.05	0.307
New onset of ILD, n (%)	0.04 ± 0.04	0.03 ± 0.05	0.512
New onset of dyspnea, n (%)	0.03 ± 0.06	0.02 ± 0.05	0.423
New onset of SRC, n (%)	0.04 ± 0.06	0.03 ± 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; ΔRRI: change in Renal Resistive Index.

Conversely, ΔRRI 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 ΔRRI 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, ΔRRI was higher than in untreated patients (0.03 ± 0.05 vs. 0.02 ± 0.05, $P = 0.033$). No significant differences of ΔRRI 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.

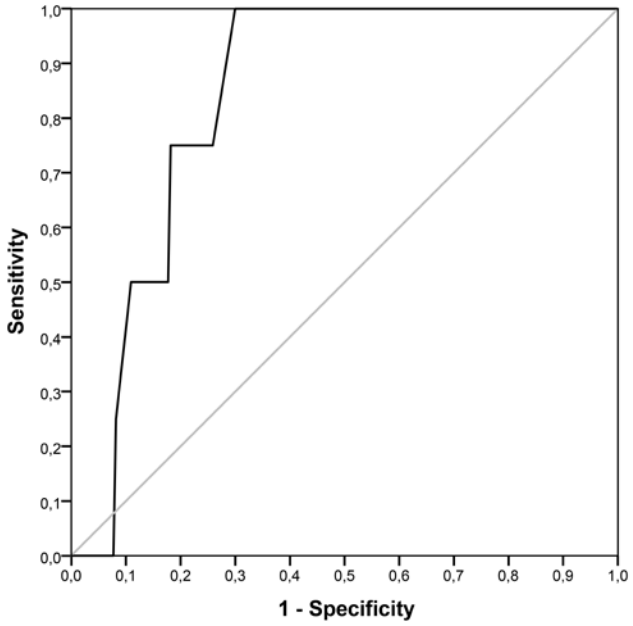

Figure 1. ROC curve for ΔRRI as predictor of new-onset PAH. PAH: pulmonary arterial hypertension; ROC: receiver-operating characteristic; ΔRRI: change in Renal Resistive Index.

DISCUSSION

Our data clearly show that the ΔRRI changed progressively during the 3.4 years of follow-up. Moreover, it correlated with ΔsPAP 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 patients[27]. 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 occurrence[6].

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 failure[2]. 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 PAH[28]. 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 ΔRRI. 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 m^2 per year. This suggests that the right heart failure might induce further renal hypoperfusion with congestion, thus promoting renal injury and eGFR decrease[29]. 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 PAH[30]. 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 PAH[30]. 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; ΔRRI: change in Renal Resistive Index.

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

	ΔRRI				$P^{\dagger}$		
	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 inhbibitor; ARB: angiotensin receptor blocker; ΔRRI: 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 m^2. 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 reduction[31]. In diabetes, the rapid increase of RRI is negatively correlated with eGFR. In our study, ΔRRI 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 suggested[13].

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 vasospasm[32]. At baseline and during follow-up, patients with SSc were treated with several drug classes. However, ΔRRI 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 ΔRRI 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 a 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.

REFERENCES

1. Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J Scleroderma Rel Disord 2017; 2:137-52.
2. Bruni C, Cuomo G, Rossi FW, Praino E, Bellando-Randone S. Kidney involvement in Systemic Sclerosis: from pathogenesis to treatment. J Scleroderma Rel Disord 2018;3:43-52.
3. Tublin ME, Bude RO, Platt JF. The resistive index in renal Doppler sonography: where do we stand? AJR Am J Roentgenol 2003;180:885-92.
4. Di Nicolò P, Granata A. Renal Resistive Index: not only kidney. Clin Exp Nephrol 2017;21:359-366.
5. Radermacher J, Chavan A, Bleck J, Vitzthum A, Stoess B, Gebel MJ, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. N Engl J Med 2001;344:410-7.
6. Rosato E, Gigante A, Barbano B, Molinaro I, Cianci R, Salsano F. Doppler indices of intrarenal arterial stiffness are useful in monitoring scleroderma renal crisis. Scand J Rheumatol 2013;42: 80-81.
7. Rosato E, Barbano B, Gigante A, Molinaro I, Quarta S, Pisarri S, et al. Increased intrarenal arterial stiffness may predict the occurrence of new digital ulcers in systemic sclerosis. Arthritis Care Res 2014;66:1380–1385.
8. Gigante A, Barbano B, Granata G, Quarta S, Amoroso A, Salsano F, et al. Evaluation of estimated glomerular filtration rate and clinical variables in systemic sclerosis patients. Clin Nephrol 2016; 85:326-331.
9. Gigante A, Barbano B, Di Mario F, Rosato E, Simonelli M, Rocca AR, et al. Renal parenchymal resistance in patients with biopsy proven glomerulonephritis: Correlation with histological findings. Int J Immunopathol Pharmacol 2016;29:469-74.
10. Ikee R, Kobayashi S, Hemmi N, Imakiire T, Kikuchi Y, Moriya H, et al. Correlation between the resistive index by Doppler ultrasound and kidney function and histology. Am J Kidney Dis 2005; 46:603–609.
11. Sugiura T, Wada A. Resistive index predicts renal prognosis in chronic kidney disease. Nephrol Dial Transplant 2009; 24:2780-2785.

12. Trostle DC, Bedetti CD, Steen VD, Al-Sabbagh MR, Zee B, Medsger TA Jr. Renal vascular histology and morphometry in systemic sclerosis. A case-control autopsy study. Arthritis Rheum 1988;31:393-400.
13. Bruni C, Maestripieri V, Rosato E, Gigante A, Tesei G, Bellando-Randone S, et al. The Renal Resistive Index in systemic sclerosis: determinants, prognostic implication and proposal for specific age-adjusted cut-offs. Eur J Intern Med. 2019; S0953:30314-0.
14. Shanmugam VK, Steen VD. Renal manifestations in scleroderma: evidence for subclinical renal disease as a marker of vasculopathy. Int J Rheumatol 2010;pii:538589.
15. Kovalchik MT, Guggenheim SJ, Silverman MH, Robertson JS, Steigerwald JC. The kidney in progressive systemic sclerosis: a prospective study. Ann Intern Med 1978;89:881-7.
16. Rosato E, Gigante A, Barbano B, Gasperini ML, Cianci R, Muscaritoli M. Prognostic Factors of Renal Involvement in Systemic Sclerosis. Kidney Blood Press Res 2018;43:682-689.
17. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737-47.
18. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis 2011;70:476-81.
19. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.
20. Suliman YA, Bruni C, Johnson SR, Praino E, Alemam M, Borazan N, et al. Defining skin ulcers in systemic sclerosis: systematic literature review and proposed World Scleroderma Foundation (WSF) definition. J Scleroderma Relat Disord 2017;2:115-20.
21. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma Rel Disord 2017;2:11-8.
22. Ruaro B, Smith V, Sulli A, Pizzorni C, Tardito S, Patané M, et al. Innovations in the Assessment of Primary and Secondary Raynaud's Phenomenon. Front Pharmacol 2019;10:360.
23. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J 2005;26:153-61.
24. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography Endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685-713.
25. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A et al; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67-119.
26. Gigante A, Rosato E, Massa R, Rossi C, Barbano B, Cianci R, et al. Evaluation of Chronic Kidney Disease Epidemiology Collaboration equation to estimate glomerular filtration rate in scleroderma patients. Rheumatology (Oxford) 2012;51:1426-31.
27. Launay D, Sobanski V, Hachulla E, Humbert M. Pulmonary hypertension in systemic sclerosis: different phenotypes. Eur Respir Rev 2017;26:170056.
28. Matucci-Cerinic M, Kahaleh B, Wigley FM. Evidence that systemic sclerosis is a vascular disease. Arthritis Rheum 2013;65:1953-62.
29. Bitker L, Sens F, Payet C, Turquier S, Duclos A, Cottin V, et al. Presence of kidney disease as an outcome predictor in patients with pulmonary arterial hypertension. Am J Nephrol 2018;47:134-143.
30. Kazory A, Ross EA. Pulmonary Arterial Hypertension and the Kidney: Getting to the Heart of the Matter. Am J Nephrol 2018; 47:130-133.
31. Boddi M, Natucci F, Ciani E. The internist and the renal resistive index: truths and doubts. Intern Emerg Med 2015;10:893-905.
32. Scorza R, Rivolta R, Mascagni B, Berruti V, Bazzi S, Castagnone D, et al. Effect of iloprost infusion on the resistance index of renal vessels of patients with systemic sclerosis. J Rheumatol 1997;24:1944-8.