

## Original Paper

# Left Ventricular Mass and Intrarenal Arterial Stiffness as Early Diagnostic Markers in Cardiorenal Syndrome Type 5 due to Systemic Sclerosis

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## Key Words

Cardiorenal syndrome · Systemic sclerosis · Renal resistive index · Left ventricular mass · Doppler ultrasound · Echocardiography

## Abstract

**Background:** Cardiorenal syndrome type 5 (CRS-5) includes a group of conditions characterized by a simultaneous involvement of the heart and kidney in the course of a systemic disease. Systemic sclerosis (SSc) is frequently involved in the etiology of acute and chronic CRS-5 among connective tissue diseases. In SSc patients, left ventricular mass (LVM) can be used as a marker of nutritional status and fibrosis, while altered intrarenal hemodynamic parameters are suggestive of early kidney involvement. **Methods:** Forty-two consecutive patients with a diagnosis of SSc without cardiac and/or renal impairment were enrolled to assess whether cardiac muscle mass can be related to arterial stiffness. Thirty subjects matched for age and sex were also enrolled as healthy controls (HC). All patients performed echocardiography and renal ultrasound. **Results:** Doppler indices of intrarenal stiffness and echocardiographic indices of LVM were significantly increased in SSc patients compared to HC. A positive correlation exists between LVM/body surface area and pulsatile index ( $p < 0.05$ ,  $r = 0.36$ ), resistive index ( $p < 0.05$ ,  $r = 0.33$ ) and systolic/diastolic ratio ( $p < 0.05$ ,  $r = 0.38$ ). Doppler indices of intrarenal stiffness and LVM indices were significantly higher in SSc patients with digital ulcers than in SSc patients without a digital ulcer history. **Conclusions:** SSc is characterized by

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the presence of microvascular and multiorgan injury. An early cardiac and renal impairment is very common. LVM and intrarenal arterial stiffness can be considered as early markers of CRS onset. The clinical use of these markers permits a prompt identification of organ damage. An early diagnosis allows the appropriate setting of pharmacological management, by slowing disease progression.

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## Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by endothelial dysfunction and fibrosis of both skin and internal organs. The hallmark of the disease is a vascular dysfunction involving both the macro- and microvasculature. SSc is a systemic disease most frequently affecting the lungs [1], heart [2], autonomic nervous system [3] and kidneys [4]. The ‘heart scleroderma’ pattern is peculiar, since, while left ventricular systolic dysfunction is present only in a small percentage of patients, a diastolic dysfunction is fairly frequent [5]. Kidney involvement in SSc includes scleroderma renal crisis, normotensive renal crisis, reduced renal functional reserves and isolated reduction in glomerular filtration rate [4]. However, since the heart and the kidney are connected one to another, having a very intense interaction, a dysfunction in one of the two organs can lead to a dysfunction of the other. Cardiorenal syndromes (CRS) are a group of disorders of the heart and the kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other. Five types of CRS have been defined by Ronco et al. [6] (table 1). The fifth type, also known as ‘secondary CRS’, encompasses a group of systemic conditions that cause simultaneous cardiac and renal dysfunction. Recently, SSc has been included among the possible etiologies of CRS type 5 (CRS-5) [7]. Our group already demonstrated that left ventricular mass (LVM), measured by echocardiography and normalized by body surface area (BSA), can be used as a marker of nutritional status and fibrosis in SSc patients [8]. Moreover, increased renal arterial stiffness is known to be associated with sclerodermic kidney dysfunction [4], and we also demonstrated that Doppler indices of intrarenal stiffness are reliable predictors of new digital ulcer occurrence [9]. Considering the strong relationship between the kidney and heart, and the frequency of simultaneous involvement of these two organs in the course of SSc, it would be clinically relevant to assess whether LVM can be related to intrarenal arterial stiffness, thus predicting a cardiorenal dysfunction before it becomes clinically evident. Therefore, the aim of our study is to define early diagnostic markers in CRS-5 due to SSc.

## Materials and Methods

### *Participants*

We enrolled 42 patients with SSc (31 women and 11 men, with a mean age of  $50 \pm 13$  years). All patients met the preliminary American College of Rheumatology/European League against Rheumatism criteria for the classification of SSc [10]. The mean durations of Raynaud’s phenomenon (RP) and disease were  $10.2 \pm 6.5$  and  $8.8 \pm 5.3$  years, respectively. Overall, 19 patients had limited cutaneous SSc (lcSSc), and 23 had diffuse cutaneous SSc (dcSSc), as defined by LeRoy et al. [11]. Table 2 shows the epidemiologic and clinical features of SSc patients and healthy controls (HC).

All SSc patients were under treatment with calcium channel blockers (nifedipine 30 mg/day). None of them were treated with immunosuppressive agents.

Patients with elevated serum creatinine (sCr), elevated blood urea, urinary tract infections, abnormal urinary sediment, glomerulonephritis, kidney stones, anti-phospholipid-associated nephropathy, diabetes, cardiovascular diseases such as hypertension, myocardial infarction, arrhythmias, heart failure, pulmonary arterial hypertension, left ventricular dysfunction, pulmonary fibrosis, interstitial lung disease, pulmonary

**Table 1.** Definition of the five subtypes of CRS

CRS-1	Acute worsening of heart function leading to AKI
CRS-2	Chronic abnormalities in heart function leading to progressive CKD
CRS-3	Acute worsening of kidney function leading to acute heart dysfunction
CRS-4	CKD leading to chronic heart disease
CRS-5	Cardiac and renal dysfunction due to acute or chronic systemic disorders

AKI = Acute kidney injury; CKD = chronic kidney disease.

**Table 2.** Epidemiological and clinical features of HC and SSc patients

	SSc	HC
Females/males	31/11	22/8
Age, years	50±13	46±15
Body mass index	22±3	22±3.8
CKD-EPI, ml/min	98±21	99±18
Systolic blood pressure, mm Hg	115±7	110±10
Diastolic blood pressure, mm Hg	70±15	73±12
mRSS	12±6.4	NA
Disease activity index	3.1±2.3	NA
DSS	5.7±3.6	NA
dcSSc/lcSSc	23/19	NA
SSc-specific autoantibodies		
Anti-topoisomerase I	24 (57.1)	NA
Anticentromere	13 (31)	
None	5 (11.9)	
Patients with a digital ulcer history	23 (54.8)	NA

Data are given as the mean ± SD or n (%). NA = Not assessed.

venous occlusive disease, chronic obstructive pulmonary diseases, hyperlipidemia, coagulopathy, scleroderma renal crisis or smokers were excluded. None of them were under treatment with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers. Thirty HC (22 females and 8 males, mean age 46 ± 15 years) were also recruited. The subjects' written consent was obtained according to the Declaration of Helsinki. The study has been approved by the Ethics Committee of Sapienza University.

*Renal Function*

Renal function was evaluated by the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [12].

*Echocardiography*

LVM (g/m<sup>2</sup>) was assessed by bidimensional M-mode echocardiography, using the Devereux regression formula [13, 14]: LVM = 0.8 × (1.04 [(LVIDd + PWTd + SWTd)<sup>3</sup> - (LVIDd)<sup>3</sup>]) + 0.6 g. According to the most recent literature, normal LVM values are ≤115 g/m<sup>2</sup> in men and ≤95 g/m<sup>2</sup> in women [15]. Patients' anthropometry (weight, height, body mass index) and biochemistry were collected from charts and recorded.

*Doppler Ultrasound*

Renal Doppler ultrasound was performed using a Toshiba Aplio Ultrasound System SSA-790 equipped with a convex 3.5-MHz probe. Renal Doppler flow was measured in 3 different interlobar arteries for each kidney guided by color-flow mapping. The following parameters were measured: peak systolic velocity, resistive index (RI), pulsatile index (PI) and systolic/diastolic ratio (S/D). RI was calculated as (peak systolic frequency shift - minimum diastolic frequency shift)/peak systolic frequency shift, and PI was calculated as

**Table 3.** Body mass index, eGFR, Doppler indices of intrarenal stiffness and LVM in SSc patients and HC

	SSc patients	HC	p
Body mass index	22±3.1	22±3.8	n.s.
CKD-EPI, ml/min	98±21	99±18	n.s.
PI	1.23±0.31	1.03±0.17	<0.01
RI	0.62±0.09	0.50±0.05	0.0001
S/D ratio	2.83±0.74	2.07±0.20	0.0001
LVM, g	143±40	91.6±24.6	0.001
LVM/BSA, g/m <sup>2</sup>	85.6±19.4	72.8±14.1	0.001

n.s. = Not significant.

(peak systolic frequency shift/minimum diastolic frequency shift)/mean frequency shift. Then, a mean value of 3 measurements obtained from interlobar arteries of different parts of both kidneys was calculated.

Weighted  $\kappa$  was used to evaluate the interrater reliability by the same observer.  $\kappa$  values for RI and S/D were 0.971 and 0.975, respectively. The intrapatient coefficient of variation for RI and S/D measurements was 1.3 and 1.4%, respectively. Calcium channel blocker therapy was discontinued 72 h before Doppler ultrasound examination. The mean reference value for normal RI in adults was determined to be  $0.60 \pm 0.10$ , with 0.70 as the upper limit of normal [16]. Patients receiving iloprost therapy underwent Doppler examination the day before the next infusion.

#### Clinical Assessment

Skin thickening was assessed by the modified Rodnan total skin score (mRSS) [17]. Disease activity was measured using Valentini's Scleroderma Disease Activity Score (SDAS) [18], and disease severity was measured with the modified Medsger Scleroderma Disease Severity Scale (DSS) [19].

#### Statistical Analysis

All results are expressed as mean and standard deviation (SD). Commercial software (SPSS version 20.0) was used for statistical analysis. The coefficient of skewness and the coefficient of kurtosis were used to evaluate the normal distribution of data. Multiple regression analysis was made to estimate the relationship between eGFR and clinical features (e.g. age or duration of disease). To determine the independent association between LVM, intrarenal stiffness and digital ulcer history, we performed a multivariate analysis, while the Bonferroni test was used in the post hoc analysis. Group comparisons were made by Student's unpaired 2-tailed t test. Pearson's product-moment correlation coefficient (r) was used to test for an association between numerical variables. The  $\chi^2$  test or Fisher's exact test, as appropriate, were used to compare categorical variables. The Mann-Whitney U test or Kruskal-Wallis test were used to test the differences between two individual study groups, and data were expressed as median and range when they were not normally distributed, due to the small sample. p values <0.05 were considered significant.

## Results

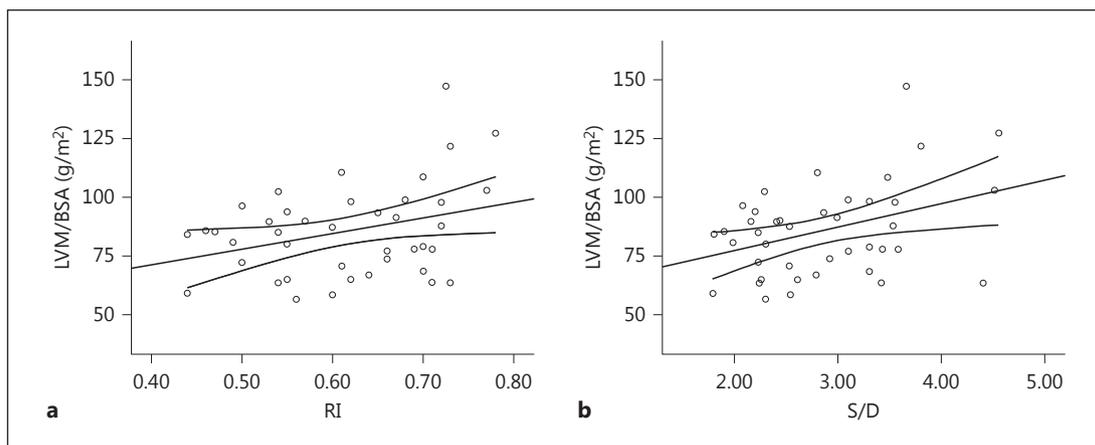
In SSc patients, eGFR using the CKD-EPI equation was  $98 \pm 21$  ml/min. The urinalysis showed normal urinary sediment in all SSc patients. In HC, the eGFR value was  $99 \pm 18$  ml/min. The mean values of Doppler indices of intrarenal stiffness in SSc patients were: PI  $1.23 \pm 0.32$ , RI  $0.61 \pm 0.09$  and S/D ratio  $2.84 \pm 0.74$ . In HC, the mean values were: PI  $1.03 \pm 0.17$ , RI  $0.50 \pm 0.05$  and S/D ratio  $2.07 \pm 0.20$ . Therefore, Doppler indices of intrarenal stiffness were significantly higher in SSc patients than in HC (table 3).

In SSc patients, the mean value of LVM was  $143.7 \pm 40.4$  g, while the LVM/BSA mean value was  $85.6 \pm 19.4$  g/m<sup>2</sup>; in HC, the LVM mean value was  $91.6 \pm 24.6$  g, while the LVM/BSA mean value was  $72.8 \pm 14.1$  g/m<sup>2</sup>. Hence, the mean values of LVM and LVM/BSA were significantly higher in SSc patients than in HC (table 3). Moreover, a statistically significant difference was

**Table 4.** Doppler indices of intrarenal stiffness and LVM in SSc patients with and those without a digital ulcer history

	SSc patients with digital ulcers	SSc patients without digital ulcers	p
LVM, g	158.8 (101.4–170)	123.3 (82–158)	<0.0001
LVM/BSA, g/m <sup>2</sup>	93.8 (65–137)	72.4 (56.6–89.6)	<0.0001
PI	1.39 (1–1.94)	1.03 (0.69–1.59)	<0.0001
RI	0.69 (0.53–0.78)	0.56 (0.44–0.71)	<0.0001
S/D ratio	3.30 (2.16–4.55)	2.30 (1.79–3.43)	<0.0001

Figures in parentheses are ranges.



**Fig. 1.** Correlation between LVM/BSA and RI (a) or S/D ratio (b) in SSc patients.

observed between males and females in both SSc patients and HC groups. In SSc patients, the mean value of LVM was significantly ( $p < 0.01$ ) higher in males ( $170.4 \pm 39.3$  g) than in females ( $134.3 \pm 36.9$  g); similarly, LVM/BSA was significantly ( $p < 0.05$ ) higher in males ( $92.1 \pm 21.1$  g/m<sup>2</sup>) than in females ( $80.1 \pm 18.5$  g/m<sup>2</sup>). In the same way, in HC, the mean value of LVM was significantly ( $p < 0.001$ ) higher in males ( $127.7 \pm 16.8$  g) than in females ( $78.4 \pm 7.7$  g), and LVM/BSA was significantly increased ( $p < 0.001$ ) in males ( $92.1 \pm 13.3$  g/m<sup>2</sup>) compared to females ( $65.8 \pm 4.6$  g/m<sup>2</sup>).

Furthermore, a positive correlation between age and LVM was observed in both SSc patients ( $r = 0.38$ ,  $p < 0.05$ ) and HC ( $r = 0.41$ ,  $p < 0.05$ ); we had a similar result for LVM/BSA in both SSc patients ( $r = 0.46$ ,  $p < 0.01$ ) and HC ( $r = 0.49$ ,  $p < 0.01$ ).

Moreover, in SSc patients, we found a positive correlation between LVM/BSA and PI ( $p < 0.05$ ,  $r = 0.36$ ), RI ( $p < 0.05$ ,  $r = 0.33$ ) and S/D ratio ( $p < 0.05$ ,  $r = 0.38$ ; fig. 1). Furthermore, a significant correlation was observed between echocardiographic LVM indices (LVM and LVM/BSA) or Doppler indices of intrarenal stiffness and different clinical variables of the disease (disease duration, mRSS, Disease Activity Index and DSS). The LVM was significantly higher ( $p < 0.0001$ ) in SSc patients with a digital ulcer history (158.8 g, range 101.4–170) than in patients with no ulcer history (123.3 g, range 82–158). Similarly, the LVM/BSA was significantly higher ( $p < 0.0001$ ) in SSc patients with a digital ulcer history (93.8 g/m<sup>2</sup>, range 65–137) than in patients with no ulcer history (72.4 g, range 56.6–89.6). In the same way, Doppler indices of intrarenal stiffness were significantly ( $p < 0.0001$ ) increased in SSc patients with a digital ulcer history compared to SSc patients with no history of ulcers (table 4).

Doppler indices of intrarenal stiffness do not show any correlation with mRSS, disease duration, SDAS or DSS. Also, echocardiographic indices of LVM do not show any correlation with mRSS, disease duration, SDAS or DSS. In two subsets of the disease (dcSSc and lcSSc), we did not find significant differences in Doppler indices of intrarenal stiffness and echocardiographic indices of LVM.

## Discussion

CRS is a condition more and more frequently observed in clinical practice [20]. Systemic diseases, such as SSc, may cause acute or chronic CRS-5. In the chronic onset, it is difficult to establish which one, either the heart or kidney, has been involved first [7].

CRS and other systemic conditions such as SSc have common pathways that lead to organ impairment. For this reason, identifying this syndrome can help in establishing the diagnostic and interventional strategies that can detect the common pathways to organ impairment in patients with predisposing factors for the onset of CRS at an early stage. Cardiac and renal involvements are common features in SSc, and an injury can develop slowly in the course of the disease. Since it is well known that protein-energy malnutrition may influence LVM, in a previous study, we have demonstrated that LVM correlates with patients' body mass index, skin thickening and the vascular domain of DSS. Furthermore, we found that patients with ulcers had a significantly greater LVM compared to patients without skin lesions. Moreover, it is well known that a clinically silent kidney injury in the course of SSc can be detected by Doppler renal ultrasound [21] and that RI correlates with systemic autonomic dysfunction [3], digital ulcers [9] and erectile dysfunction [22]. After analyzing our results, we can postulate that LVM/BSA correlates with intrarenal arterial stiffness as demonstrated by elevated RI, PI and S/D. In particular, we demonstrated that Doppler indices of intrarenal stiffness and LVM/BSA are increased in SSc patients compared to HC. In addition, Doppler indices of intrarenal stiffness are increased in SSc patients with a digital ulcer history compared to patients with no history of ulcers. Increased intrarenal arterial stiffness can be considered the first manifestation of vascular renal scleroderma impairment, and it correlates with the eGFR trend [21]. Following the relationship between intrarenal arterial stiffness and capillaroscopic damage, Rosato et al. [9] demonstrated that scleroderma renal damage starts with an injury of the microvascular vessels. In addition, it has been demonstrated that response to vasodilator drugs correlates with intrarenal arterial Doppler indices [23]. In an autoptic study, Follansbee et al. [24] demonstrated that SSc patients had a greater prevalence of both advanced myocardial fibrosis (60%) and contraction band necrosis (40%) than HC. The authors concluded that in SSc patients, myocardial fibrosis is consistent with the presence of microvascular coronary vasospasm, a cardiac RP. Hence, these results suggest that a structural damage of vasculature occurs in many vascular districts and contributes to cardiac and renal dysfunction. RP is the hallmark of SSc and represents the clinical expression of a blood vessel spasm in the fingers, heart, kidney and other internal organs [25, 26, 9]. Therefore, a diffuse RP could be considered as the trigger for chronic CRS-5. We examined both patients with early and late stages of disease. The vascular complication of disease (digital ulcer history) demonstrated an association with Doppler indices of intrarenal stiffness and echocardiographic indices of LVM. In agreement with literature data, the vascular hypothesis plays a key role in the pathogenesis of renal and cardiac damage in asymptomatic SSc patients.

Furthermore, apart from RP, cardiorenal involvement is supported by an increase in proinflammatory cytokines and increased levels of angiotensin II that result in a profibrotic, procoagulatory, atherogenic and arrhythmogenic state and raise oxidative stress leading to further cardiac and renal damage [27].

Echocardiography and Doppler renal ultrasound can provide useful information for an early diagnosis and management of CRS in the course of SSc. The limitation of traditional markers such as sCr has to be taken into account in the setting of CRS. In particular, an underestimated GFR reduction can be present in SSc patients despite a normal or even low sCr due to muscle mass wasting [8]. The strength of our study is increased by the exclusion of patients with chronic kidney disease and cardiovascular abnormalities, so our results were not influenced by other conditions other than SSc. However, our limitation is the small sample size that can weaken the power of our study, even though our results are statistically significant. Therefore, we can conclude that LVM and intrarenal arterial stiffness can be used as early markers of CRS in the course of SSc.

Until today, there are no tests that evaluate kidney damage in SSc patients with normal renal function (sCr and urinary sediment) or cardiac dysfunction in SSc patients without pulmonary hypertension or diastolic dysfunction. Since the vascular hypothesis could play a key role in the pathogenesis of CRS-5, the therapy with vasoactive drugs (e.g. prostanoids) can be early started in SSc patients with increased Doppler indices of intrarenal stiffness or echocardiographic indices of LVM. Further studies with a bigger population are warranted, since an early diagnosis allows a prompt setting of pharmacological management to slow the progression of the damage.

### Disclosure Statement

The authors have no conflicts of interest to declare.

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