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Original article

Ultrasound evaluation of bowel vasculopathy in systemic sclerosis

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ABSTRACT

Background: Gastrointestinal (GI) manifestations are frequent in systemic sclerosis (SSc) with an impact on quality of life and morbidity. Bowel vasculopathy is a key pathogenetic factor responsible for GI involvement. **Objectives:** To compare abdominal ultrasound (US) and Color Doppler Ultrasonography (CDU) features of splanchnic vessels of SSc patients with healthy controls.

Methods: The charts of SSc patients who underwent an abdominal US and CDU study were retrospectively analyzed. For Superior Mesenteric Artery (SMA) and Inferior Mesenteric Artery (IMA) caliber, Peak Systolic Velocity (PSV), Reverse Velocity (RV), End-Diastolic Velocity (EDV), Mean Velocity (mV), Blood-flow, Resistive Index (RI) and Pulsatility Index (PI) were recorded.

Results: 28 SSc patients and 28 controls were enrolled. In SSc, caliber of SMA was significantly smaller than in controls (5.75 ± 0.62 mm vs. 6.45 ± 0.60 mm, $p < 0.0001$ - p adj = 0.0002). The flow study of SMA and IMA showed a significant reduction of RV (SMA: 7.25 ± 6.37 cm/s vs. 18.52 ± 6.16 cm/s, $p < 0.0001$ - p adj < 0.0001; IMA: 2.69 ± 6.10 cm/s vs. 17.06 ± 5.75 cm/s, $p < 0.0001$ - p adj < 0.0001) and PI (SMA: 3.33 ± 0.75 vs. 4.53 ± 1.03 , $p < 0.0001$ - p adj = 0.0002; IMA: 3.54 ± 0.95 vs. 6.08 ± 1.53 , $p < 0.0001$ - p adj < 0.0001) in SSc patients than controls.

Conclusion: involvement of splanchnic vessels in SSc may be non-invasively investigated with abdominal US and CDU. Morphological and functional changes of Doppler parameters observed in SMA and IMA clearly demonstrate that these vessels are affected by SSc vasculopathy.

1. Introduction

Systemic sclerosis (SSc) is a complex disease with a heterogeneous clinical spectrum and a complex pathophysiology characterized by immune activation and diffuse microvascular injury resulting in internal organ fibrosis [1,2].

In SSc, gastrointestinal (GI) involvement occurs in more than 90% of

patients [3]. It does not spare any tract of GI system, from the oral cavity, down to the esophagus, stomach, small and large bowels [4] as well as the liver and pancreas, causing several clinical manifestations [5–7]. Although GI involvement may be the cause of death in only 12% of cases [8], it is a major source of morbidity in SSc [9].

In the literature, a large number of studies have focused the attention on the vascular involvement in the main organs, like heart, kidneys,

The members of the Study Group of Rheumatology and Internal Medicine are listed in the Appendix

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lungs and skin [10–14]. In the mucosa of the stomach and duodenum, modifications of blood flow have been observed with endoscopic laser Doppler flowmetry [15]. However, few papers have investigated vascular abnormalities of small and large bowels (i.e. superior and inferior mesenteric circulation). In fact, the involvement of the circulation of this tract may be correlated to motility impairment, which is the main cause of stasis, bowel dilatation with bacterial overgrowth, malabsorption, weight loss and also a decreased survival rate [8,16,17].

Gastrointestinal imaging with plain radiographs and barium studies, ultrasound, computed tomography and magnetic resonance imaging is helpful in detecting involvement of GI system [18]. Abdominal Ultrasound (US) offers the opportunity to examine non-invasively the bowel, including extra-intestinal features such as the splanchnic vessels, mesentery and lymph nodes [19]. This technique has a good accuracy and repeatability for properly trained users [20,21]. Moreover, Color Doppler Ultrasonography (CDU) assesses the signal from the visceral vessels that supply the GI tract, analyses the superior and inferior mesenteric arteries by pulsed Doppler scanning and can provide several quantifiable parameters (systolic, mean and diastolic velocities, resistance and pulsatility indexes, blood flow volume) [22,23]. The normal fasting flow in the superior mesenteric artery (SMA) has been assessed in a large number of studies while there is less data found on the flow parameters in the inferior mesenteric artery (IMA) [24–26].

The purpose of our work was to investigate SMA and IMA blood flow in SSc patients with abdominal US and CDU to identify the morphological and functional modifications of the vascular splanchnic district.

2. Materials and methods

Patients classified as SSc (ACR/EULAR 2013 classification criteria) and with a complete clinical record, followed in the Rheumatology Division of the Azienda Ospedaliero Universitaria Careggi, were identified. A retrospective review of the clinical charts of the SSc patients was performed and those who underwent a complete abdominal US and CDU of SMA and IMA were enrolled. From the clinical charts information about demographic data (age, sex) were also collected. Healthy subjects who performed an abdominal ultrasound at the Internal Medicine Unit of the same Hospital were used as controls. Patients with a history of peripheral/coronary arterial disease were excluded.

The complete abdominal US and CDU study of the SMA and IMA was usually performed after a fasting of at least 8 h in all subjects. The US investigation was conducted at Maggiore Hospital of Bologna, by a single operator blinded to disease features. The US and CDU examination of SMA and IMA blood flow was performed with an Esaote Mylab 70 Twice using a 3.5–5 MHz Convex probe for a panoramic view of abdominal organs and splanchnic arteries and a 5–12 MHz Linear probe for the accurate measurement of caliber, thickness and **echogenicity** of abdominal vessels.

The caliber was measured 25 mm after the emergence from abdominal aorta for SMA and 15 mm after the emergence from the abdominal aorta for IMA; Doppler parameters were measured 15 mm after the emergence from the abdominal aorta for both arteries. The position of the probe was adjusted to reach an angle of less than 60° and the sample volume was corrected to include the entire inner diameter of the vessel. Every measurement was the mean of three consecutive determinations.

For both SMA and IMA, the following parameters were measured:

- caliber (mm),
- Doppler parameters:
 - o Peak Systolic Velocity - PSV (cm/s),
 - o Reverse Velocity - RV (cm/s),
 - o End-Diastolic Velocity - EDV (cm/s),
 - o Mean Velocity - mV (cm/s),
 - o Blood-flow (ml/min),
- Semi-quantitative indexes:

Table 1

Baseline characteristics of SSc patients.

Patients characteristics	Results	N
Gender (n;%)		28
females	25 (89.30%)	
males	3 (10.70%)	
Age (mean $\pm$ SD)	48.75 (12.93) years	28
Disease duration (median; IR)	7 (2–9) years	23
Autoantibodies (n;%)		
ANA	27 (100%)	27
ACA	6 (23.08%)	26
Scl70	19 (70.37%)	27
RNA pol III	1 (3.85%)	26
GI symptoms (n;%)		22
reflux	11 (50.00%)	
dysphagia	3 (13.64%)	
abdominal bloating	5 (22.73%)	
diarrhea	4 (18.18%)	
stipsis	1 (4.55%)	
fecal incontinence	2 (9.10%)	
bacterial overgrowth	0 (0%)	
malabsorption	0 (0%)	
DU (n;%)		
present	3 (12.00%)	25
in the past	15 (60.00%)	25
NVC pattern (n;%)		11
early	2 (18.18%)	
active	7 (63.64%)	
late	2 (18.18%)	
ILD (n;%)	15 (65.22%)	23
PAH (n;%)	5 (26.31%)	19
Vasodilators/vasoactive treat. (n;%)		
sildenafil	5 (17.86%)	28
pentoxifylline	4 (14.29%)	28
cardioaspirin	4 (14.29%)	28
ACE-i	3 (10.71%)	28
CCBs	8 (28.57%)	28
beta-blockers	3 (10.71%)	28
iloprost	5 (17.86%)	28
alprostadil	2 (7.14%)	28
Immunosuppressors/immunomodulants (n;%)		
HCQ	6 (21.42%)	28
MTX	1 (3.57%)	28
AZA	1 (3.57%)	28
MMF	8 (28.57%)	28
RTX	3 (10.71%)	28
CYC	2 (7.14%)	28
IVIg (n;%)	5 (17.86%)	28
Steroids (n;%)	8 (28.57%)	28

(N = number of patients; SD = standard deviation; IR = interquartile range; DU = digital ulcers; GI = gastrointestinal; NVC = nailfold videocapillaroscopy; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; ACE-i = angiotensin-converting enzyme inhibitors; CCBs = calcium channel blockers; HCQ = hydroxychloroquine; MTX = methotrexate; AZA = azathioprine; MMF = mycophenolate mofetil; RTX = rituximab; CYC = cyclophosphamide; IVIg = intravenous immunoglobulin)

- o Resistive Index – RI $(PSV - EDV/PSV)$,
- o Pulsatility Index – PI $(PSV - EDV/mV)$.

The study protocol and patients signed informed consent were approved by local IRB (19,907.oss).

For continuous variables we reported mean and standard deviation; absolute frequency and percentage of any category was calculated for categorical variables. In order to evaluate the difference between groups for every parameter adjusted for age a multiple linear regression model was used. The statistical significance level was set at 5%. Mean differences between the two groups for every parameter has been evaluated with T-test. All the tests were adjusted for age. A *p* value < 0.05 was considered significant.

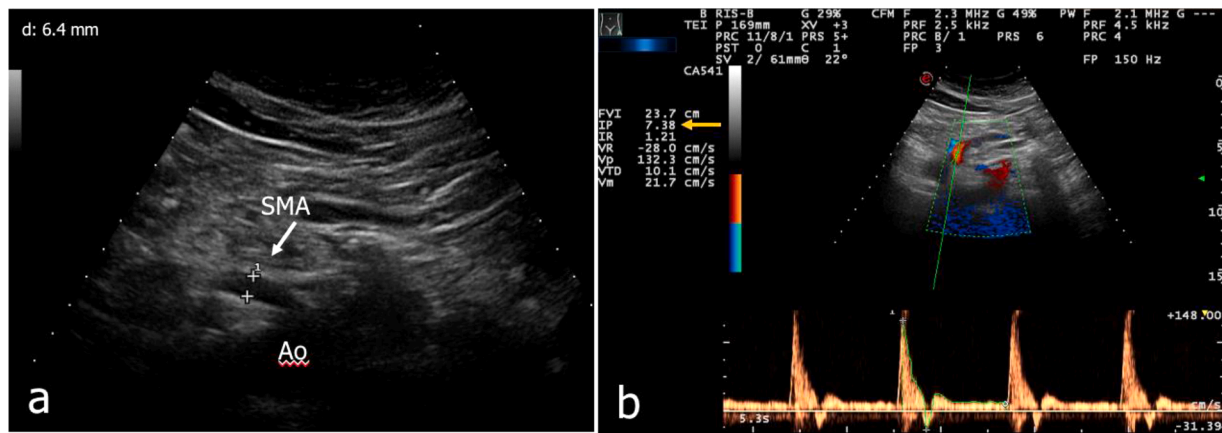


Fig. 1. Superior Mesenteric Artery (SMA): Normal morphological (a) and shape of Doppler wave and Doppler flow parameters (b) in healthy control subject, in which the negative diastolic component of Doppler spectrum is typical of the normal SMA, with high PI (Pulsatility Index; yellow arrow); Ao: Abdominal aorta (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

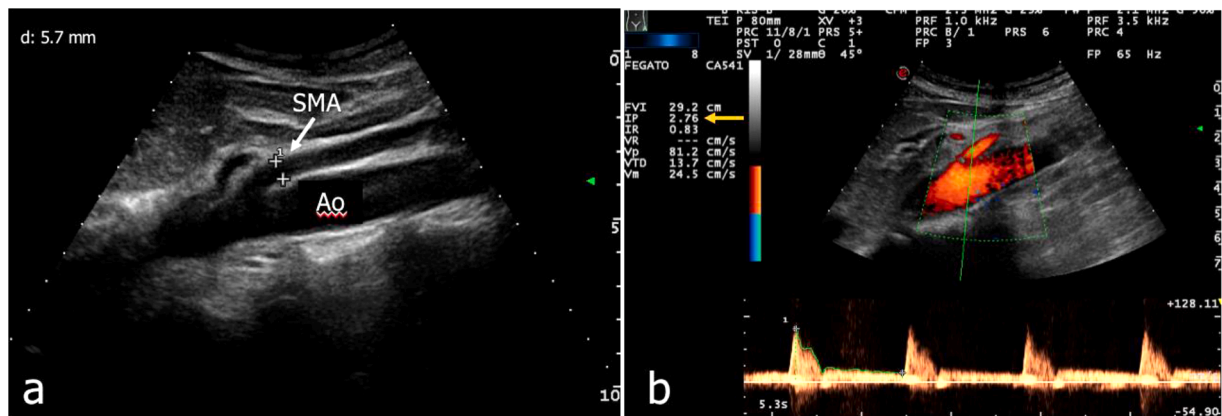


Fig. 2. Superior Mesenteric Artery (SMA): SSc morphological (a) and shape of Doppler wave and Doppler flow parameters (b) in SSc patient. In (b) the negative diastolic component of Doppler spectrum of the normal SMA is lacking, with low PI (Pulsatility Index; yellow arrow); Ao: Abdominal aorta (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

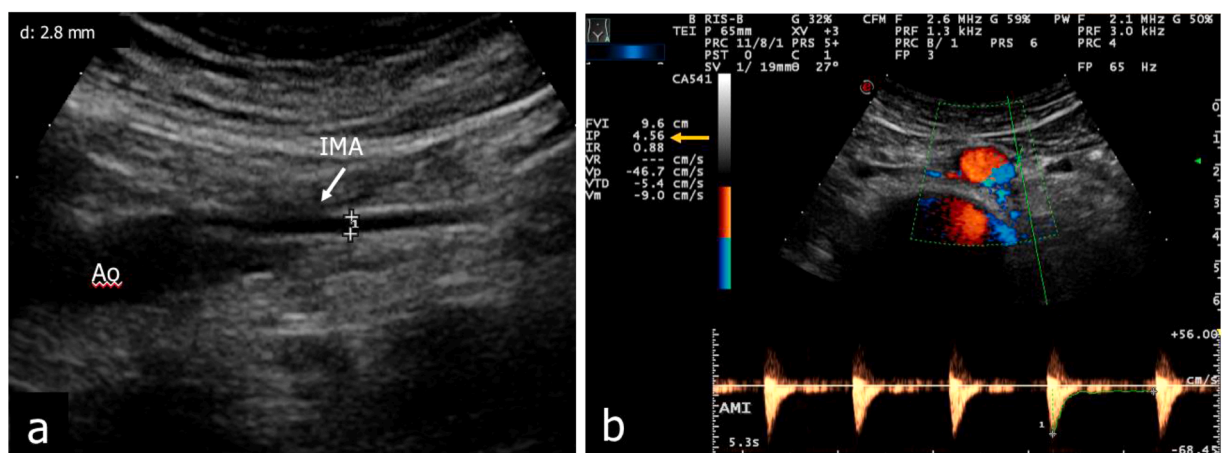


Fig. 3. Inferior Mesenteric Artery (IMA): Normal morphological (a) and shape of Doppler wave and Doppler flow parameters (b) In healthy control subject, in which the normal little negative diastolic component of Doppler spectrum is typical of the IMA, with high PI (Pulsatility Index; yellow arrow); Ao: Abdominal aorta (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

3. Results

Among a cohort of 89 SSc patients, 28 had US and CDU data available. The patients were mainly females (25 females, 89.3%), with a

mean age of 48.75 ± 12.39 years. In the control group, 28 subjects were identified [18 females (64.3%), 10 males (35.7%), with a mean age of 36.25 ± 12.08 years]. In Table 1 the main baseline characteristics of the SSc cohort are presented.

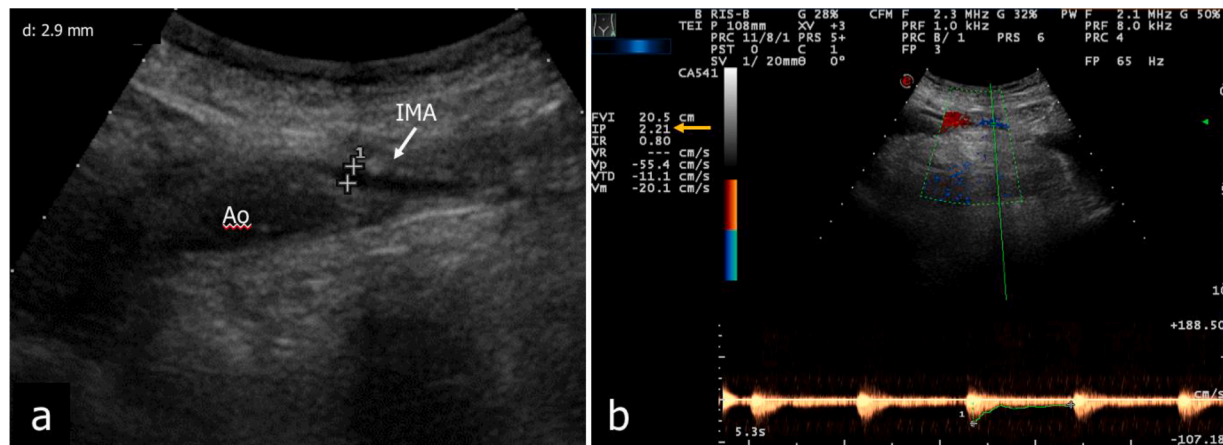


Fig. 4. Inferior Mesenteric Artery (IMA): SSc morphological (a) and shape of Doppler wave and Doppler flow parameters (b) in SSc patient in which the normal little negative diastolic component of Doppler spectrum is very low and with low PI (Pulsatility Index; yellow arrow); Ao: Abdominal aorta (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

Table 2

Comparison of the characteristics of SMA and IMA between SSc patients and controls.

	SSc		Controls		p-value	Age adjusted p-value (p _{adj} -value)
SMA	N	Mean ± SD	N	Mean ± SD		
Caliber (mm)	28	5.75 ± 0.62	28	6.45 ± 0.60	<0.0001	0.0002
PSV (cm/s)	28	137.50 ± 34.50	28	135.26 ± 33.81	0.8075	0.7297
RV (cm/s)	28	7.25 ± 6.37	28	18.52 ± 6.16	<0.0001	<0.0001
EDV (cm/s)	28	16.34 ± 7.03	28	12.64 ± 5.46	0.0321	0.0650
mV (cm/s)	28	38.03 ± 13.90	28	28.32 ± 9.25	0.0035	0.0150
Blood-flow (cm/s)	28	1073.1 ± 831.16	28	913.36 ± 272.87	0.3409	0.4781
PI	28	3.33 ± 0.75	28	4.53 ± 1.03	<0.0001	0.0002
RI	28	0.88 ± 0.04	28	0.91 ± 0.03	0.0034	0.0141
IMA	N	Mean ± SD	N	Mean ± SD		
Caliber (mm)	26	2.71 ± 0.47	24	2.79 ± 0.37	0.4872	0.5385
PSV (cm/s)	23	72.27 ± 27.23	23	93.81 ± 25.73	0.0084	0.0044
RV (cm/s)	23	2.69 ± 6.10	23	17.06 ± 5.75	<0.0001	<0.0001
EDV (cm/s)	23	7.87 ± 2.01	23	7.95 ± 2.10	0.8921	0.9250
mV (cm/s)	23	17.83 ± 5.33	23	14.75 ± 5.08	0.0514	0.3938
Blood-flow (cm/s)	23	106.70 ± 47.99	20	84.00 ± 30.13	0.0676	0.3056
PI	23	3.54 ± 0.95	23	6.08 ± 1.53	<0.0001	<0.0001
RI	23	0.88 ± 0.04	23	0.91 ± 0.03	0.0132	0.0205

(PSV = Peak Systolic Velocity; RV = Reverse Velocity; EDV = End-Diastolic Velocity; mV = Mean Velocity; RI = Resistive Index; PI = Pulsatility Index; SMA = superior mesenteric artery; IMA = inferior mesenteric artery; N = number of patients; SD = standard deviation).

From the cardiovascular point of view, 2 SSc patients presented systemic arterial hypertension and 1 patient had dyslipidemia.

In the fasting state, the shape of Doppler wave was different between SSc patients and healthy controls as the early negative diastolic component typical of normal SMA and IMA flow was reduced (sometimes even absent) in the majority of SSc patients (Figs. 1–4).

Table 2 summarizes the results of our analysis, with adjustment for age. Although the control group was significantly younger than the SSc group ($p = 0.0003$), all the results were confirmed after adjustment for age.

The flow study of both SMA and IMA confirmed a significant reduction of RV in SSc patients when compared to controls (SMA: 7.25 ± 6.37 cm/s vs. 18.52 ± 6.16 cm/s, $p < 0.0001$ - $p_{adj} < 0.0001$; IMA: 2.69 ± 6.10 cm/s vs. 17.06 ± 5.75 cm/s, $p < 0.0001$ - $p_{adj} < 0.0001$) (Fig. 5).

The mean PI was significantly lower in SSc patients than in controls both for SMA and for IMA (SMA: 3.33 ± 0.75 vs. 4.53 ± 1.03 , $p < 0.0001$ - $p_{adj} = 0.0002$; IMA: 3.54 ± 0.95 vs. 6.08 ± 1.53 , $p < 0.0001$ - $p_{adj} < 0.0001$) (Fig. 6).

Similar results were obtained for RI which was lower in patients than controls for both vessels (SMA: 0.88 ± 0.04 vs. 0.91 ± 0.03 , $p = 0.0034$ - $p_{adj} = 0.0141$; IMA: 0.88 ± 0.04 vs. 0.91 ± 0.03 , $p = 0.0132$ - $p_{adj} = 0.0205$).

The flow study of SMA showed a significant increase of mV (38.03 ± 13.90 cm/s vs. 28.32 ± 9.25 cm/s, $p = 0.0035$ - $p_{adj} = 0.0150$) and of EDV (16.34 ± 7.03 cm/s vs. 12.64 ± 5.46 cm/s, $p = 0.0321$) when compared to healthy controls. However, the EDV increase was not statistically significant after adjustment for age ($p_{adj} = 0.0650$). On the contrary, the flow study of IMA did not reveal any difference in EDV and mV between the two groups; SSc patients showed a reduction of PSV (72.27 ± 27.23 cm/s vs. 93.81 ± 25.73 cm/s, $p = 0.0084$ - $p_{adj} = 0.0044$) when compared to controls.

In SSc patients, the caliber of SMA was significantly smaller than in controls (5.75 ± 0.62 mm vs. 6.45 ± 0.60 mm, $p < 0.0001$ - $p_{adj} = 0.0002$). No difference in IMA caliber was found between SSc and controls.

4. Discussion

Our data clearly show that splanchnic vessels may be affected in SSc patients, determining an alteration of the main Doppler parameters related to vascular impedance and elasticity, both for SMA and IMA. These results were obtained with CDU, which is a feasible, non-invasive and repeatable technique.

As we know from the literature, GI involvement is present nearly in 90% of SSc patients, potentially affecting the whole gastrointestinal

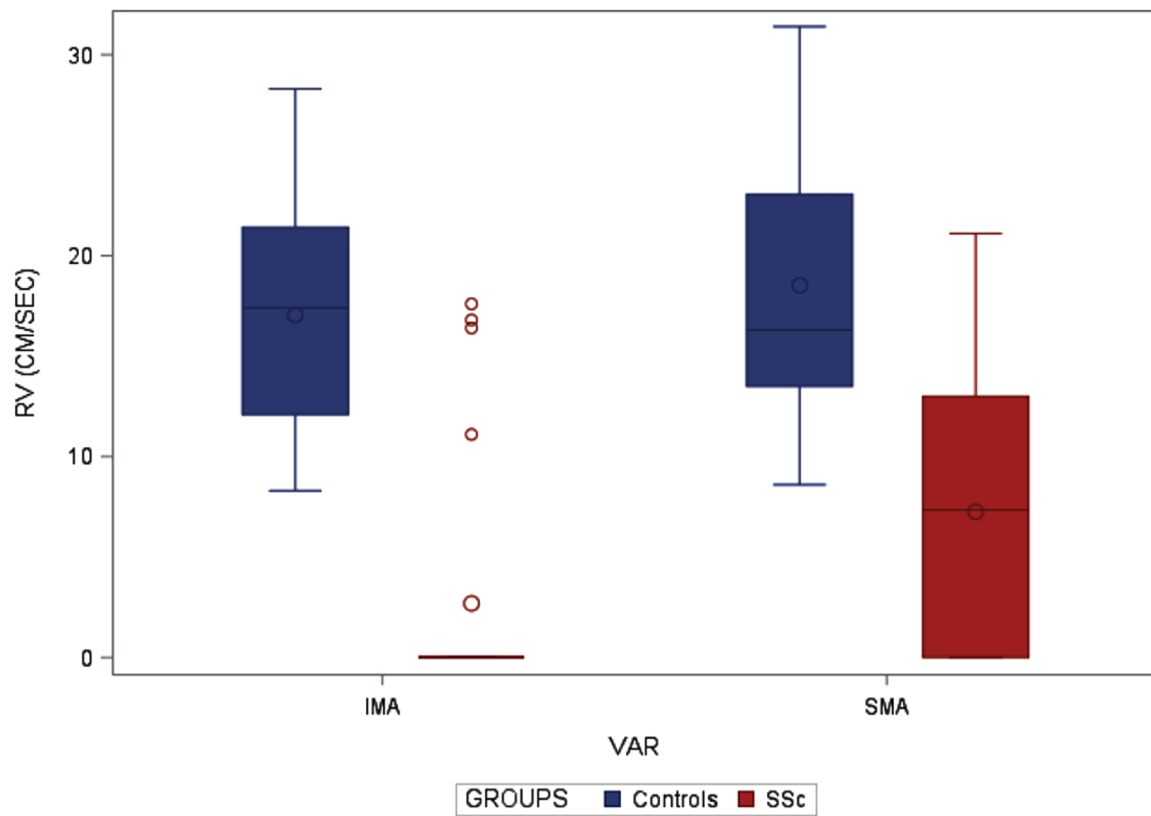


Fig. 5. Distribution of RV of IMA and SMA between groups.

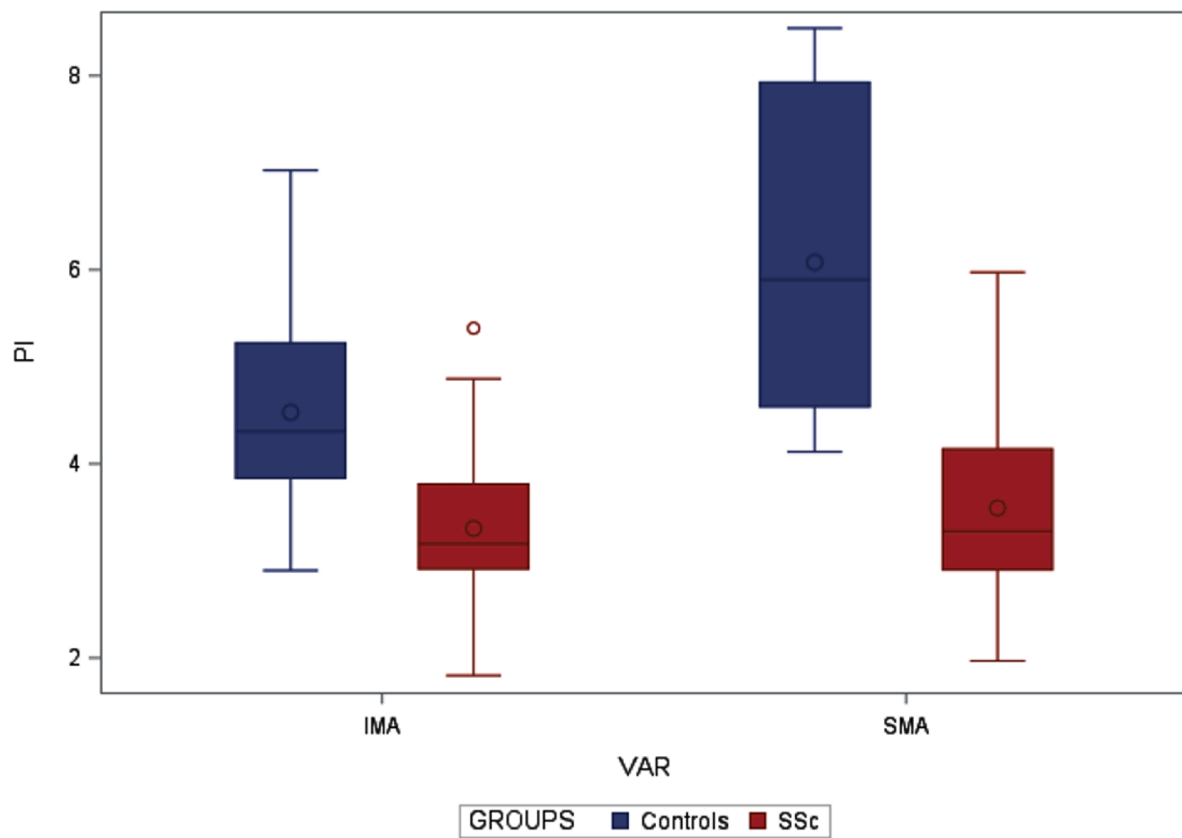


Fig. 6. Distribution of PI of IMA and SMA between groups.

tract. Morbidity associated with small and large bowel involvement can severely debilitate patients [9,27]. In 1999, Medsger et al. proposed a disease severity scale for such specific organ involvement [28,29]. Despite the clinical relevance of GI involvement and related symptoms in the course of the disease, in the past decades the main attention has been focused on other organs involvement [10–14]. Moreover, up to date the development of severe malabsorption confers 50% of increased mortality at 8.5 years, and the management of GI involvement still remains empirical and symptom-driven [30–32].

It is well known that in the esophagus, the stomach and the small bowel, the vasculature modification and blood flow impairment are crucial events, potentially explaining the evolution to fibrosis and the thickening of bowels walls [33,34]. Several hypotheses suggest that an initial vascular insult at GI level may lead to neurogenic dysfunction and bowel dysmotility prior to definitive structural changes [2]. In 2002, Ibba Manneschi et al. showed specific modifications of the vessels of the stomach and rectum, with clear evidence of ultrastructural alterations of endothelial cells [35].

However, considering that the large part of small and large bowel is vascularized by mesenteric circulation, there are only few works in the literature addressing the involvement of this vascular district.

Several papers report the significant haemodynamic effects of Iloprost infusion on hepatic perfusion and portal flow velocity and volume [36,37], whereas few studies have been carried out on the involvement of splanchnic circulation. In 2005, Salera et al. have shown that iloprost infusion reduced RI of SMA, together with a significant hemodynamic effect on portal flow [38].

Overall, only one study focused the attention on mesenteric flow in SSc. The Doppler parameters of SMA were measured in 27 patients without severe clinical manifestations: in the fasting state, a significant difference in the shape of SMA Doppler wave form was found, as the early negative diastolic component was absent [39]. The authors found a significantly lower mean SMA diameter and blood flow and a lower mean PI was described without reaching statistical significance. In fasting SSc patients, the study showed changes in basal hemodynamics caused by vasoconstriction of the SMA, detectable even in the absence of any GI symptom. Moreover, the disappearance of SMA vasoconstriction under the effects of a balanced meal stimulation may likely suggest a preclinical functional condition probably correlated to an increased vascular sympathetic activity.

In our study, a complete evaluation of the splanchnic circulation was performed by measuring the morphological and functional parameters of SMA and IMA. As far as we know, IMA has never been investigated in SSc, despite the fact that it vascularizes a large part of the bowel and that reduction of its blood flow is often the cause of major GI complications. Even though it is not easy to study the IMA in all patients, because of its small diameter and its anatomical course, we believe it is absolutely crucial to have a complete picture of splanchnic circulation in the attempt to understand its real role in the pathogenesis of GI involvement in SSc.

Our results are in agreement with previous data that found an absent early negative diastolic component of blood flow of SMA [39]. In fact, in the majority of our patients, the early negative diastolic component of SMA blood flow was absent or significantly reduced, confirming the alteration of the Doppler wave form of this splanchnic artery. Moreover, in our patients we accurately measured also the IMA blood flow parameters, and found the same significant reduction of RV and PI, both confirming a modification of the main Doppler parameters related to vascular impedance. Clearly, these data reflect an alteration of the arterial elasticity in the whole splanchnic district of SSc patients.

It is to be noticed that a single operator performed all the abdominal evaluations and, considering that US is an operator-dependent technique, this could be a limit for the accuracy of our data. It might be interesting to include in the protocol another independent operator and to examine the inert-observer reliability of these parameters, in order to obtain more solid results.

As a future agenda, the measurement of mesenteric blood flow could be performed with a balanced liquid meal to recognize early functional pathological modifications of blood flow. Moreover, it could be very interesting to study this splanchnic district with the help of contrast-enhanced ultrasound for a better morphological, structural and functional evaluation of mesenteric arteries. In addition, association with gastrointestinal manifestations, as well as with patient reported outcomes capturing gastrointestinal affections, may further support the usefulness of abdominal CDU.

In the future, all these information may support the basis of a new therapeutic approach to the GI system, not only symptom-driven but targeted on early vascular involvement of splanchnic circulation, possibly impacting on the progression of SSc-induced GI.

5. Conclusion

In conclusion, these preliminary data suggest that, as for other target organs, in the splanchnic district of SSc patients the vasculature is significantly affected, paralleling the SSc GI involvement. The possibility to explore the whole mesenteric circulation with a non-invasive and feasible technique such as US and CDU might be clinically relevant in the early phases of the disease, when only mild symptoms are observed.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Appendix

Collaborators of the Study Group of Rheumatology and Internal Medicine: Gargani Luna, Institute of Clinical Physiology, National Research Council, Pisa; Cappelli Francesco, Interventional and structural cardiology, heart, lung and vessels department AOU Careggi; Perfetto Federico, Department of Experimental and Clinical Medicine, University of Florence, and Division of Internal

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