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COMMENT

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Endotheliopathy in systemic sclerosis: from endothelium-dependent vasodilation to the dysfunction of the vascular reserve, *is the paradise lost?*

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Abstract

Microvascular dysfunction is considered one of the main pathogenetic pathways in systemic sclerosis (SSc), and endothelial cells plays a pivotal role even in the early phases of the disease. Endothelial dysfunction results in an early incapacity to adapt the vascular tone and the blood flow under stress conditions, thus losing the important adaptation mechanism that is the vascular reserve.

The loss of vascular tone control in systemic sclerosis is clinically evident as Raynaud's phenomenon, one of the earliest signs of the disease. An impairment of the vascular reserve has been described in the literature for the main SSc target organs. An alteration of the *coronary reserve* was shown in SSc asymptomatic patients undergoing a provocative cardiac stress tests. For what concerns the *pulmonary circulation*, in presence of normal resting pulmonary pressure values in specific subsets of SSc patients subjected to a cycle ergometer test, an abnormal elevation of pulmonary pressure has been showed. Regarding *renal arterial circulation*, in SSc patients with normal baseline renal function, an absence of improved glomerular filtration after the infusion of a protein load has been demonstrated. Finally, vascular reserve can be altered even in the *gastrointestinal circulation* as assessed by the study of the splanchnic circulation after a balanced meal.

An early detection of an alteration of the physiologic protective mechanism of the vascular reserve could open a "window of opportunity" in which SSc vasculopathy can be potentially reversible, and more responsive to targeted therapeutic strategies.

Keywords Systemic sclerosis, Vascular reserve, Endotheliopathy, Endothelial dysfunction

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Systemic sclerosis (SSc) is a chronic and progressive systemic autoimmune disease involving the skin and the internal organs, characterized by a complex pathogenesis [1]. One of the main pathogenetic pathways is the microvascular dysfunction which, associated with an autoimmune dysregulation and an uncontrolled fibroblast activation, leads to abnormal collagen production resulting into skin and organ fibrosis. In the pathogenetic cascade, the temporal dynamic of interactions between the immune system, the endothelium, the fibroblasts and the autonomic nervous system still remains to be elucidated. However, endothelial cells (EC) are considered to play a pivotal role as their dysfunction is considered a main event in the very early phase of SSc [2]. The disruption of the integrity of the EC layer is the underlying cause of several critical diseases and it is well known that EC, covering the subendothelial layer, are part of a system which is physiologically adapting to several conditions that may jeopardize the main function of keeping vessel patency. Indeed, endothelial cells, which line the interior of blood vessels and cover the subendothelial layer, form a dynamic and adaptable system that, under physiological conditions, adjusts to multiple stimuli or stressors in order to preserve one of its main roles: maintaining vascular patency and preventing occlusion. Therefore, the EC health is of paramount relevance to maintain the homeostasis of the vasoconstriction/vasodilating balance in the microvascular system. This unique ability is maintained by the "endothelial reserve" which, upon any constrictive stimulation or activation/damage, still keeps the vessel patency thus maintaining the required blood flow. Thus, the concept of **"vascular reserve"** is a fundamental physiological mechanism of organ protection that, under conditions of increased demand, allows to increase the vascular perfusion at an ubiquitous level. In the vascular reserve, two main mechanisms mantain the balance in the control of the vascular tone, namely (i) the ability to adapt to oxidative stress and (ii) the endothelium-dependent vasodilation [3] which is mainly kept by endothelium-derived substances like nitric oxide. In SSc, these functions have been shown to be progressively lost, in particular due to chronic oxidative stress [4, 5]. Therefore, in the pathogenetic cascade the **endothelial dysfunction** (ED) seems to be the earliest event misbalancing vascular tone control, [6, 7] and later substantially contributing to accelerated atherosclerosis [7, 8]. The hallmark of ED is the impairment of endothelium-dependent vasodilation which is the mainstay of the vascular reserve. Early stage ED is termed "Endotheliopathy" referring to the functional and/or anatomical changes in EC [9]. These modifications may lead to a wide molecular response which is clinically expressed through a wide number of illnesses [10]. At the EC level, two molecular pathways are predominantly activated, the inflammatory and the microthrombotic ones. Actually, SSc pathogenesis appears to follow a chronological progression, with the inflammatory pathway being predominant in the early disease phase, while the microthrombotic pathway takes the lead much later [11]. The EC react both to continuous aggression by reactive oxygen species and cytokines derived from inflammatory and immune cells, leading not only to ED and damage but also to the loss of EC adaptation and of the precious endothelium-dependent vasodilation. The net effect is the loss of vascular tone control, clinically evident as Raynaud's phenomenon (RP), which is considered the earliest sign, often present long before the appearance of other clinical SSc features. Moreover, it is widely believed that EC damage and RP may also occur in internal organs (i.e. heart, lung, kidney, and the gastrointestinal tract), leading to frequent ischemia-reperfusion episodes that trigger the transition of fibroblasts, EC and pericytes into myofibroblasts and the thickening of the vascular wall [12]. In practice, the fight against this chain of pathogenetic events, which originate from the microcirculation in all organs, should start as early as possible, before functional alterations become irreversible due to definitive structural modifications (Fig. 1).

In the literature, the earliest report on altered vascular reserve in SSc concerns the coronary circulation. A clear alteration of the coronary reserve was shown in SSc patients undergoing provocative physical or pharmacologic testing who were completely asymptomatic and with no instrumental and biohumoral alterations that could be correlated with resting coronary ischemia [9, 13]. In the following years, several studies confirmed a specific and selective alteration of coronary reserve in SSc [14, 15, 16, 17, 18, 19, 20].

In 2011, our group studied the vascular reserve of the renal arterial circulation in SSc patients with normal indices of renal function, assessed through the standard biohumoral parameters (i.e. creatinine and urea) and through the calculation of glomerular filtrate using the Cockroft formula. Our data showed that a subset of patients were unable to achieve an appropriate arteriolar vasodilation and a consequent increase in glomerular filtrate, after the infusion of a protein load [21]. These data clearly demonstrated a significant alteration of renal vascular reserve in SSc patients.

In SSc, data from the literature provide the evidence for a progressive loss of the regulation of the mechanism of vascular reserve also at the level of the pulmonary circulation, which is crucial in determining patients survival as pulmonary hypertension heavily impacts on patients' life expectancy [22]. For more than 20 years, the "exercise-induced pulmonary hypertension" has been investigated and an increase in the normal resting pulmonary pressure values above the cut offs was found in SSc patients subjected to a cycle ergometer test [23, 24, 25, 26]. In

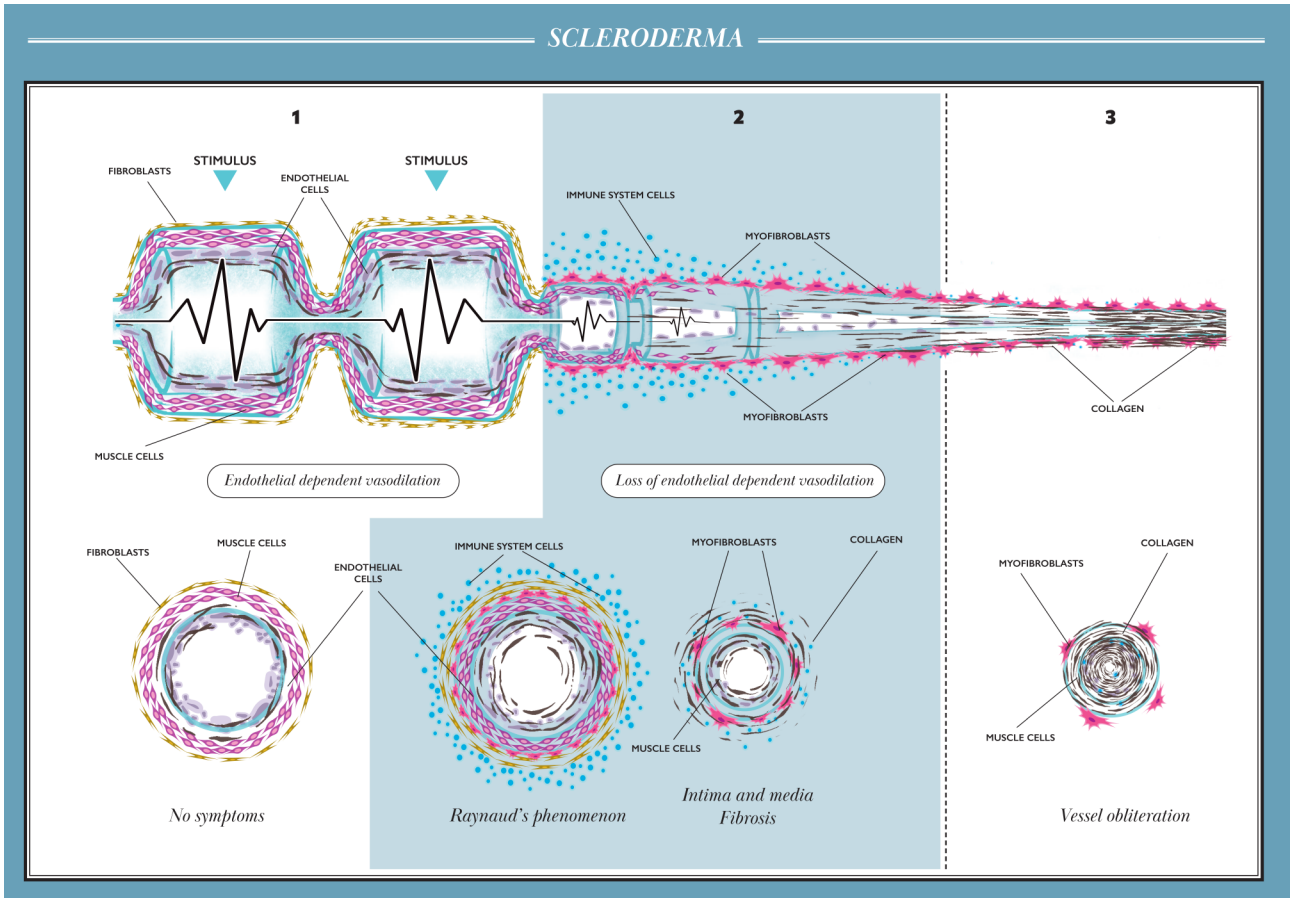

Fig. 1 Endothelium-dependent vasodilation and the loss of vascular reserve

fact, some authors have highlighted that SSc patients, without any alteration of left heart function and no signs of interstitial lung disease, showed values of pulmonary pressure at peak exertion clearly out of threshold, when subjected to physical exertion. These results clearly suggest an intrinsic dysfunction of the vascular reserve in SSc patients at the level of the pulmonary circulation [25, 26]. This behaviour was measured using both indirect non-invasive (i.e. echocardiography) and direct (i.e. right catheterization) measurements of pulmonary pressures [27, 28]. The findings demonstrated that asymptomatic SSc patients may have at rest normal pulmonary pressure values that under conditions of increased demand, like physical exertion, lack the capacity to adapt and maintain stable pulmonary pressure values. Thus, these data provide the evidence that in SSc a dysfunction of the vascular reserve may be detected also at the level of the pulmonary circulation.

Moreover, also in the gastrointestinal system, an early dysfunction of the splanchnic circulation, covering the vascular flow requirements of the entire intestinal tract, has been described [29]. Previously, we have shown that in SSc patients the entire splanchnic circulation may be investigated with doppler ultrasound that may detect a flow modification in both the superior and the inferior mesenteric arteries [30]. In SSc, an impairment of the splanchnic circulation compared to healthy controls was detected in response to a balanced meal [31]. Moreover, the failure of the increase of the splanchnic flow suggested an early dysfunction of the vascular compensation mechanisms, physiologically activated in response to food intake. This evidence has led to the hypothesis that an early dysfunction of the vascular reserve may indicate a vascular modification which precedes the clinical manifestations, arising much later due to the progression of the SSc gastrointestinal involvement.

In the skin vessels, the involvement of the endothelium as well as vessels' wall thickening have been shown, but no studies have functionally addressed the loss of endothelial adaptation. However in the skin at the extremities, the most prominent hallmark of vascular dysfunction is Raynaud's phenomenon which is characterized by a triphasic expression (white, blue, red) according to the vessel patency [32, 33]. These three colors clearly represent the chain of events (closure of the vessels, ischemia and reperfusion, respectively), but also the red phase testifies

the capacity of the endothelium to adapt and counteract the stimuli restoring the vessel patency. However, the progression of endotheliopathy, the loss of endothelial adaptation along with the vessel wall thickening eventually provoke, due to the lowering of blood flow, a chronic blue cyanosis, definitively substituting the functional triphasic phenomenon.

Collectively, these data highlight the fact that in SSc an early pathophysiologic event is already activated, priming a dysregulation of vascular adaptation with an impairment of the compensatory mechanisms in the skin and multiple internal organs that in basal conditions still maintain a normal function. In this early SSc phase, it might be hypothesized that the ED may be still reversible in case a targeted therapeutic strategy is chosen to obtain disease remission. This approach may protect the endothelial homeostasis, the vascular tone control and, in particular, the modulation of the balance between vasoconstricting and vasodilating factors. Clearly, the best efforts of SSc investigators are today focused on the very early diagnosis of SSc (VEDOSS) patients, in whom, being the vascular signs and symptoms predominant, the modulation of the progression of vasculopathy may be much easier.

Therefore, in a clinical setting the assessment of organ vascular reserve in SSc could open a "window of time" in which an ED-targeted therapy would have the potential for greater long-term efficacy. The crucial capacity of EC to keep the patency of blood vessels is such an important function of protection that should not be overlooked by physicians caring for SSc. The deterioration of the vascular reserve can be compared to a ***'Paradise Lost'*** as it may clearly define the transition from reversible to irreversible ED. This condition should warn the clinician not to overlook a crucial opportunity that the disease itself offers in its pathophysiological course. In fact, in the early SSc stage, characterized by microcirculatory EC damage, the protective mechanism of the "endothelial reserve" is already lost, before any signs or symptoms of organ damage are clinically evident. Therefore, a "window of opportunity" in the natural history of SSc may exist and is characterized by ED (as pathogenetic item) and RP (as clinical item) that may be potentially reversible and, therefore, more responsive to targeted therapeutic strategies. Hence, an early vascular screening should be performed in SSc patients through non-invasive assessments of vascular reserve in different organs. Likely, a prompt therapy might attenuate ED and recover the main control of the vascular tone, also in internal organs either with vasodilatory or vasoactive drugs [34].

In the next future, studies on large SSc patients cohorts in the pre-SSc and very early phase of the disease [35] are warranted to understand the mechanisms of progression of the vascular wall remodelling.

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A.M.P., M.M.C. and G.B. contributed significantly to the conception and drafting of the work. S.B.R., M.M. and L.D. have substantially revised it. All authors approve the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

Consent to Publish
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Competing interests
The authors declare no competing interests.

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References

1. Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J Scleroderma Relat Disord. 2017;2:137–52.
2. Chora I, Romano E, Manetti M, Mazzotta C, Costa R, Machado V, Cortez A, Bruni C, Lepri G, Guiducci S, De Paulis A, Soares R, Matucci-Cerinic M. Evidence for a derangement of the microvascular system in patients with a very early diagnosis of systemic sclerosis. J Rheumatol. 2017;44(8):1190–7.
3. Lu D, Maulik N, Moraru II, Kreutzer DL, Das DK. Molecular adaptation of vascular endothelial cells to oxidative stress. Am J Physiol. 1993;264:C715–722.
4. Andreucci E, Margheri F, Peppicelli S, Bianchini F, Ruzzolini J, Laurenzana A, Fibbi G, Bruni C, Bellando-Randone S, Guiducci S, Romano E, Manetti M, Matucci-Cerinic M, Calorini L. Glycolysis-derived acidic microenvironment as a driver of endothelial dysfunction in systemic sclerosis. Rheumatol Oxf. 2021;60(10):4508–19.
5. Kahaleh BM, Sheng F, Matucci Cerinic M, Stefanovic Racic M, Ignarro L. Study of the endothelial dependent relaxation in scleroderma. Arthritis Rheumatol. 1993;36(suppl):B233.
6. Pacholczak-Madej R, Kuszmiersz P, Bazan-Socha S, Kosałka-Wêgiel J, Iwaniec T, Zarêba L, Kielczewski S, Rams A, Walocha JA, Musiał J, Dropiński J. Endothelial dysfunction in patients with systemic sclerosis. Postepy Dermatol Alergol. 2020;37(4):495–502.
7. González-Martín JJ, Novella-Navarro M, Calvo-Aranda E, Cabrera-Alarcón JL, Carrión O, Abdelkader A, Aramburu F, Alcocer P, Sainz F. García de La Peña P. Endothelial dysfunction and subclinical atheromatosis in patients with systemic sclerosis. Clin Exp Rheumatol. 2020;38(3):48–52.
8. Bartoli F, Blagojevic J, Bacci M, Fiori G, Tempestini A, Conforti ML, Guiducci S, Miniati I, Di Chicco M, Del Rosso A, Perfetto F, Castellani S, Pignone A. Cerinic MM Flow-mediated vasodilation and carotid intima-media thickness in systemic sclerosis. Ann N Y Acad Sci. 2007;1108:283–90.
9. Kahan A, Devaux JY, Amor B, Menkès CJ, Weber S, Nitenberg A, Venot A, Guérin F, Degeorges M, Roucayrol JC. Nifedipine and thallium-201 myocardial perfusion in progressive systemic sclerosis. N Engl J Med. 1986;314(22):1397–402.
10. Cardenas A, Dong JC, Kozar JF. Injury-induced endotheliopathy: what you need to know. J Trauma Acute Care Surg. 2023;1(4):454–63.

11. Marongiu F, Ruberto MF, Marongiu S, Matucci Cerinic M, Barcellona D. A journey to vasculopathy in systemic sclerosis: focus on haemostasis and thrombosis. Clin Exp Med. 2023;23(8):4057–64.
12. Romano E, Rosa I, Fioretto BS, Matucci-Cerinic M, Manetti M. New insights into profibrotic myofibroblast formation in systemic sclerosis: when the vascular wall becomes the enemy. Life Basel Switz. 2021;11(7):610.
13. Vignaux O, Allanore Y, Meune C, Pascal O, Duboc D, Weber S, Legmann P, Kahan A. Evaluation of the effect of Nifedipine upon myocardial perfusion and contractility using cardiac magnetic resonance imaging and tissue doppler echocardiography in systemic sclerosis. Ann Rheum Dis. 2005;64(9):1268–73.
14. Dumitrescu D, Oudiz RJ, Karpouzas G, Hovanesyan A, Jayasinghe A, Hansen JE, Rosenkranz S. Wasserman K.Developing pulmonary vasculopathy in systemic sclerosis, detected with non-invasive cardiopulmonary exercise testing. PLoS ONE. 2010;5(12):e14293.
15. Sulli A, Ghio M, Bezante GP, Deferrari L, Craviotto C, Sebastiani V, Setti M, Barsotti A, Cutolo M, Indiveri F. Blunted coronary flow reserve in systemic sclerosis. Rheumatol (Oxford). 2004;43(4):505–9.
16. Montisci R, Vacca A, Garau P, Colonna P, Ruscazio M, Passiu G, Iliceto S, Mathieu A. Detection of early impairment of coronary flow reserve in patients with systemic sclerosis. Ann Rheum Dis. 2003;62(9):890–3.
17. Zanatta E, Famoso G, Boscain F, Montisci R, Pigatto E, Polito P, Schiavon F, Iliceto S, Cozzi F, Doria A, Tona F. Nailfold avascular score and coronary microvascular dysfunction in systemic sclerosis: A newsworthy association. Autoimmun Rev. 2019;18(2):177–83.
18. Pintér T, Faludi R, Magyari B, Vorobcsuk A, Kumánovics G, Minier T, Czirják L, Komócsi A. Mechanism of coronary flow reserve reduction in systemic sclerosis: insight from intracoronary pressure wire studies. Rheumatol Oxf Engl. 2011;50(4):781–8.
19. Feher A, Boutagy NE, Oikonomou EK, Thorn S, Liu YH, Miller EJ, Sinusas AJ, Hinchcliff M. Impaired myocardial flow reserve on 82Rubidium positron emission tomography/computed tomography in patients with systemic sclerosis. J Rheumatol. 2021;48(10):1574–82.
20. Faccini A, Agricola E, Oppizzi M, Margonato A, Galderisi M, Sabbadini MG, Franchini S, Camici PG. Coronary microvascular dysfunction in asymptomatic patients affected by systemic sclerosis - limited vs. diffuse form. Circ J. 2015;79(4):825–9.
21. Livi R, Guiducci S, Perfetto F, Ciuti G, Grifoni E, Conforti L, Galluccio F, Moggi Pignone A, Matucci Cerinic M. Lack of activation of renal functional reserve predicts the risk of significant renal involvement in systemic sclerosis. Ann Rheum Dis. 2011;70(11):1963–7.
22. Hachulla E, Carpentier P, Gressin V, Diot E, Allanore Y, Sibilia J, Launay D, Mouthon L, Jego P, Cabane J, de Groote P, Chabrol A, Lazareth I, Guillevin L, Clerson P, Humbert M. ItinérAIR-Sclérodermie study investigators. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinérAIR-Sclérodermie study. Rheumatology (Oxford). 2009;48(3):304–8.
23. Pignone A, Mori F, Pieri F, Oddo A, Galeota G, Fiori G, Del Rosso A, Perfetto F, Becucci A, Livi R, Tempestini A, Benvenuti C, Gramigna L, Fedi R, Generini S, Minelli M, Cinelli M, Guiducci S, Arcangeli C, Conforti ML, Bernardo P, Cerinic MM. Exercise doppler echocardiography identifies preclinic asymptomatic pulmonary hypertension in systemic sclerosis. Ann N Y Acad Sci. 2007;1108:291–304.
24. Steen V, Chou M, Shanmugam V, Mathias M, Kuru T, Morrissey R. Exercise-induced pulmonary arterial hypertension in patients with systemic sclerosis. Chest. 2008;134(1):146–51.
25. D'Alto M, Ghio S, D'Andrea A, Pazzano AS, Argiento P, Camporotondo R, Allocca F, Scelsi L, Cuomo G, Caporali R, Cavagna L, Valentini G, Calabrò R. Inappropriate exercise-induced increase in pulmonary artery pressure in patients with systemic sclerosis. Heart. 2011;97(2):112–7.
26. Gargani L, Gargani L, Pignone A, Agoston G, Moreo A, Capati E, Badano LP, Doveri M, Bazzichi L, Costantino MF, Pavellini A, Pieri F, Musca F, Muraru D, Epis O, Bruschi E, De Chiara B, Perfetto F, Mori F, Parodi O, Sicari R, Bombardieri S, Varga A, Cerinic MM, Bossone E, Picano E, et al. Clinical and echocardiographic correlations of exercise-induced pulmonary hypertension in systemic sclerosis: a multicenter study. Am Heart J. 2013;165(2):200–7.
27. Kovacs G, Maier R, Aberer E, Brodmann M, Scheidl S, Hesse C, Troester N, Salmhofer W, Stauber R, Fuerst FC, Thonhofer R, Ofner-Kopeinig P, Gruenig E, Olschewski H. Assessment of pulmonary arterial pressure during exercise in collagen vascular disease: echocardiography vs right-sided heart catheterization. Chest. 2010;138(2):270–8.
28. Kovacs G, Olschewski H. Potential role of exercise echocardiography and right heart catheterization in the detection of early pulmonary vascular disease in patients with systemic sclerosis. J Scleroderma Relat Disord. 2019;4(3):219–24.
29. Bandini G, Monami M, Ciuti G, Mercatelli P, Lo Cricchio A, De Santis MC, Bonomi F, Bellando Randone S, Campochiaro C, El Aoufy K, Ruaro B, Giuggioli D, Hughes M, McMahan ZH, Benfaremo D, Moroncini G, Maconi G, Accogli E, Dagna L, Matucci Cerinic M, Moggi Pignone A. Doppler ultrasound, a noninvasive tool for the study of mesenteric arterial flow in systemic sclerosis: a cross-sectional study of a patient cohort with review and meta-analysis of the literature. Intern Emerg Med. 2024 Oct;16. https://doi.org/10.1007/s11739-024-03783.
30. Bandini G, Cometi L, Accogli E, Domanico A, Tofani L, Bruni C, Bellando-Randone S, Lepri G, Orlandi M, Guiducci S, El-Aoufy K, Ciuti G, Fabbri A, Matucci-Cerinic M, Moggi-Pignone A. Study group of rheumathology and internal medicine. Ultrasound evaluation of bowel vasculopathy in systemic sclerosis. Eur J Intern Med. 2022;100:62–8.
31. Di Quarto F, Rivolta R, Berruti V, Caronni M, Bazzi S, Scorza R. Superior mesenteric artery blood flow in systemic sclerosis patients. Rheumatology (Oxford). 2002;41(7):730–4.
32. Matucci Cerinic M, Kahaleh B, Wigley F. Evidence that systemic sclerosis is a vascular disease. Arhritis Rheum. 2013;65:1953–62.
33. Pauling JD, Allanore Y, Buch MH, Cutolo M, Del Galdo F, Denton C et al. Exploiting a unified vascular framework to predict organ-specific complications and accomplish disease-modification in systemic sclerosis. Lancet Rheumatol 2025 in press.
34. Allanore Y, Meune C, Vignaux O, Weber S, Legmann P, Kahan A. Bosentan increases myocardial perfusion and function in systemic sclerosis: a magnetic resonance imaging and Tissue-Doppler echography study. J Rheumatol. 2006;33(12):2464–9.
35. Lescoat A, Bellando-Randone S, Campochiaro C, Del Galdo F, Denton CP, Farrington S, Galetti I, Khanna D, Kuwana M, Truchetet ME, Allanore Y, Matucci-Cerinic M. Beyond very early systemic sclerosis: Deciphering prescleroderma and its trajectories to open new avenues for preventive medicine. Lancet Rheumatol. 2023;5(11):e683–94.

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