Inquadramento vascolare nella SSc

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SSD Reumatologia

A.O. r.n. "G.Rummo"

Benevento

Systemic sclerosis

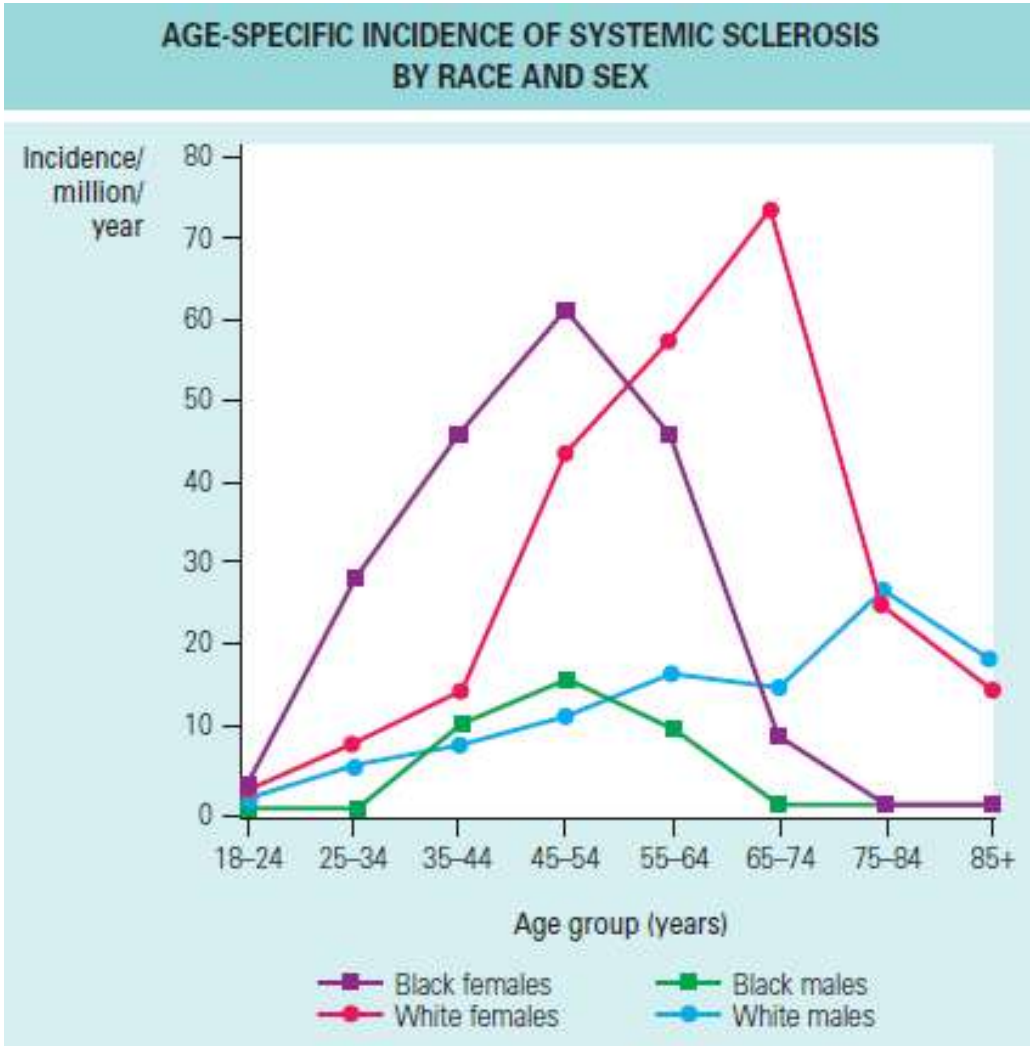
- Systemic sclerosis is a heterogeneous disease whose pathogenesis is characterized by 3 hallmarks: small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction leading to increased deposition of extracellular matrix.
- The clinical manifestations and the prognosis of SSc vary, with the majority of patients having skin thickening and variable involvement of internal organs.
- Subsets of SSc can be discerned, i.e., limited cutaneous SSc, diffuse cutaneous SSc, and SSc without skin involvement.

van den Hoogen F et al. 2013 classification criteria for systemic sclerosis: an ACR/EULAR collaborative initiative. Arthritis Rheum. 2013 Nov;65(11):2737-47

SSc incidence and prevalence

- ***prevalence rate*** of SSc varies from **4** cases per million population for the period 1947 to 1952 to **443** cases per million in 2003 in North America.
- Similarly, the ***annual incidence*** rates vary between **2.7** cases per million for the time period 1947 to 1968 to **21** cases per million for the time period 1989 to 1991.

SSc incidence by race and sex

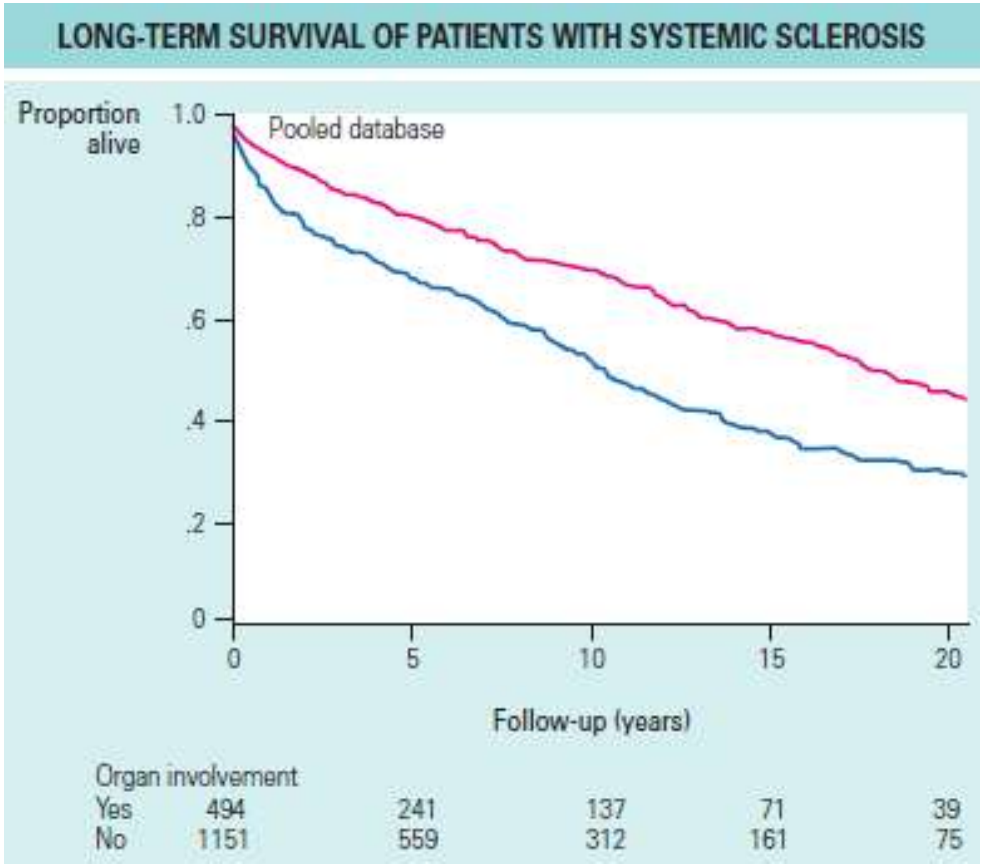


Mayes MD, Lacey JV Jr, Beebe-Dimmer J, et al.
Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large U.S. population.
Arthritis Rheum 2003;48:2246-2255

Mortality in SSc

- An international meta-analysis of individual patient data in regard to mortality in SSc has been reported among 1645 incident cases.Patients were recruited from seven medical centers in the United States, Europe, and Japan, using standardized definitions for organ involvement.
- All cohorts showed significantly increased standardized mortality ratios comparisons based on age- and sex-matched country-specific life tables.
- However, the mortality ratios varied widely, ranging from **1.5 to 7.2**, depending on country and referral base of involved center.

Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med 2005;118:2-10.



Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med 2005;118:2-10.

SSc: clinical features

Feature	Anti-centromere	Anti-topoismerase	Anti-RNA polymerase III
Limited cutaneous	Common	Less common	Less common
Diffuse cutaneous	Very rare	Common	More common
Interstitial lung disease (severe)	Rare	Common	Less common
Scleroderma renal crisis	Rare	Less common	More common
Pulmonary arterial hypertension	Common in long-standing disease	Unclear	Unclear

from: Rheumatology, 5° Edition – Mosby Philadelphia, 2011 – Section 10: M. Mayes, S. Assassi, pp. 1313-1318

Review Article

Cardiovascular disease in systemic sclerosis

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Abstract: Cardiovascular (CV) system involvement is a frequent complication of autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). It still remains unclear if a premature atherosclerosis (ATS) occurs even in systemic sclerosis (SSc). Although microvascular disease is a hallmark of SSc, in the last few years a number of studies highlighted a higher prevalence of macrovascular disease in SSc patients in comparison to healthy individuals and these data have been correlated with a poorer prognosis. The mechanisms promoting ATS in SSc are not fully understood, but it is believed to be secondary to multi-system organ inflammation, endothelial wall damage and vasculopathy. Both traditional risk factors and endothelial dysfunction have been proposed to participate to the onset and progression of ATS in such patients. In particular, endothelial cell injury induced by anti-endothelial antibodies, ischemia/reperfusion damage, immune-mediated cytotoxicity represent the main causes of vascular injury together with an impaired vascular repair mechanism that determine a defective vasculogenesis. Aim of this review is to analyse both causes and clinical manifestations of macrovascular involvement and ATS in SSc.

Keywords: Atherosclerosis (ATS); cardiovascular (CV) disease; systemic sclerosis (SSc)

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Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown etiology characterized by three hallmarks: (I) vasculopathy with the pathognomonic microvascular involvement; (II) fibrosis of skin and visceral organs; (III) systemic inflammation characterized by the presence of circulating autoantibodies and pro-inflammatory cytokines (1,2).

Studies have consistently shown a substantially increased mortality in SSc with a pooled standardized mortality ratio ranging between 2.7 and 3.5. In particular, cardio-pulmonary complications, including pulmonary arterial hypertension and interstitial lung disease, represent the main causes of reduced life expectancy and death in these patients (3).

Indeed, it has been widely demonstrated that patients with autoimmune disease, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), present a higher mortality risk mainly for cardiovascular (CV) events. In this setting, acceleration of subclinical atherosclerotic damage has been advocated as the main mechanism leading to this increased risk. However, etiopathogenesis underlying atherosclerotic wall damage is still under investigation. A close interplay between traditional CV risk factors and inflammatory and autoimmune markers may contribute to both induction and progression of atherosclerosis (ATS) in these patients (4-8).

It remains still unclear whether accelerated ATS occurs even in SSc and studies aimed to investigate subclinical ATS risk in scleroderma patients produced contrasting data. In comparison to SLE and RA, accelerated ATS appears to have a different prevalence in SSc. Moreover, the inflammatory component seems to be less prominent and ATS less aggressive in SSc, making more difficult to demonstrated subclinical ATS in these patients.

Data derived from studies carried out in 60's and 70's, when the main cause of death was scleroderma renal crisis,

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Cardiovascular disease in systemic sclerosis

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Cardiovascular disease in systemic sclerosis

- Prevalence of CV and macrovascular disease has been demonstrated to be increased in SSc patients in comparison to healthy individuals and correlated with a poorer prognosis (1, 2) and, actually, 20-30% of deaths in SSc patients are attribuitable to CV causes.
- In particular, the 2010 survey from the European League Against Reumatism Scleroderma Trials and Research (EUSTAR) database estimated that 26% of SSc-related causes of death were due to cardiac causes (mainly heart failure and arrhytmias) and 29% of non-SSc-related causes of death were due to CV causes (3).

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3. Tyndall AJ, Bannert B, Vonk M, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809-15.

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SPECIAL ARTICLE

2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

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2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

2013 Classification Criteria for Systemic Sclerosis

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti-Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

Methods for vascular assessment

- Assessment of aortic pulse wave velocity (PWV);
- Carotid intima-media thickness (IMT);
- Brachial flow-mediated dilation (FMD);
- Digital peripheral artery tonometer (EndoPAT) assessment;
- Laser speckle contrast imaging (LSCI);
- Power Doppler ultrasonography(PDu);
- Angiography (AGy).

Aortic pulse wave velocity (PWV)

- **Pulse wave velocity** (PWV) is a measure of arterial stiffness. It is easy to measure with cardiovascular magnetic resonance (CMR) or by measuring carotid–femoral pulse wave velocity (PWV) using SphygmoCor CPVH.
- A hand-held high-fidelity **SphygmoCor tonometer** is placed over the carotid and then the femoral arteries to record pressure waves simultaneously along with ECG tracings. The length of the descending aorta was approximated by subtracting the manubrium–carotid artery distance from the manubrium–femoral artery distance using a caliper. PWV in m/s was calculated in an automated fashion by proprietary software

Carotid intima-media thickness (IMT)

- **Intima-media thickness** (**IMT**), is a measurement of the thickness of tunica intima and tunica media, the innermost two layers of the wall of an artery. The measurement is usually made by external ultrasound and occasionally by internal, invasive ultrasound catheters;
- IMT is used to detect the of presence atherosclerotic disease in humans and, more contentiously, to track the regression, arrest or progression of atherosclerosis.
- Carotid IMT is assessed through B-mode ultrasound imaging on both right and left common carotid arteries. Scanning is performed from the far walls of the distal common carotid arteries of each side to the far walls of the carotid bulbs using a linear array transducer with frequency of 3–10 MHz. The lumen-intima interface was measured electronically across a 1 cm segment. **IMT score in an average obtained**.

Evaluation of carotid artery intima-media complex thickness as a marker of vascular damage secondary to accelerated atherogenesis in progressive systemic sclerosis

Avaliação da espessura do complexo médio-intimal da artéria carótida como marcador de aterogênese acelerada secundária a dano vascular na esclerose sistêmica progressiva

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ABSTRACT

Objective: To evaluate the intima-media thickness of the common carotid artery in patients with and without scleroderma; to verify a possible association with disease severity; to assess the relationship of intima-media thickness with known cardiovascular risk factors. **Methods:** In a case - control study, thirty patients with scleroderma and 30 without the disease were selected and matched according to age, sex and cardiovascular risk factors such as hypertension, diabetes mellitus and hypercholesterolemia. The age ranged from 17 to 79 years (mean 49). All patients underwent carotid artery evaluation by high-resolution vascular Doppler in order to measure the intima-medial thickness of the carotid 2 cm from the bifurcation. In all the analysis was considered the greatest value of intima-media thickness in right and left carotid arteries. **Results:** The sample consisted of 30 patients, 29 (96.67%) women and one man (3.3%). In this sample, 11/30 (36.67%) had high blood pressure, 5/30 (16.67%) had diabetes mellitus, 6/30 (20%) had dyslipidemia and 2/30 (6.67%) were smokers. Comparing the measure of the increased risk (maximum intima-media thickness between the left and right side), was obtained an average of 0.77 mm for group scleroderma and a value of 0.70 mm for the control group ($p = 0.21$). In assessing the association between disease severity and carotid intima-media thickness, was found no significant association ($p= 0.925$). **Conclusion**: Was found a slight increase in intima-medial thickness of common carotid artery in patients with scleroderma but without statistical significance. Regarding the severity of the disease and intima-medial thickness of common carotid artery, there was no significant difference.

Key words: Patients. Scleroderma, systemic. Carotid arteries. Atherosclerosis. Carotid intima-media thickness.

INTRODUCTION

Systemic scleroderma is an autoimmune rheumatic disease that has vascular injury as one of its main clinical markers[1]. This injury is an important cause of increased morbidity, mortality and loss in quality of life of this group of patients[1]. Some possible mechanisms responsible for ischemic events are vasospasm, endothelial damage by immune activity and abnormalities of glucose homeostasis[2]. It is believed that the interaction of genetic predisposition to the stimulation of environmental factors can lead to vascular dysfunction and ischemia resulting in tissue fibrosis in advanced stages of disease [2].

The most obvious clinical manifestation and early vascular involvement is Raynaud's phenomenon, which occurs as the first manifestation in 70% of patients and in up to 95% of cases over the course of the disease[4]. It is defined as an abnormal vasoconstrictor response to cold that causes episodes of recurrent spasms of the digital arteries, arterioles and cutaneous arterio-venous shunts. It is observed that a significant reduction in blood flow can occur leading to complete closure of the vessel lumen[5]. All these changes can cause chronic tissue hypoxia and irreversible tissue damage, with the formation of recurrent ulcers, fibrosis and, in severe cases, gangrene or even amputation of the extremities[5].

Although the microvascular involvement is a marker of systemic scleroderma, the involvement of macrovasculature or macrovascular disease is also often associated with significant morbidity and mortality [6]. However this latter form of vascular involvement in scleroderma is not widely accepted, although some authors have described this association[6].

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Brachial flow-mediated dilation (FMD)

- Brachial arte h is used **to assess endothelial** ted methods:

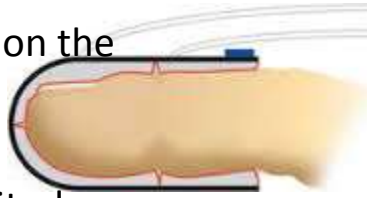
1. assessmer a) by ultrasound before and rtery induced by pneumatic than systolic blood pressure, f ency of 3–10 MHz and
2. endothelia ore and after 0.4 mg of sublingu pray into the mouth. Brachial ar ne, 1, 2 and 3 minutes after react the forearm and at 3, 5 and 10 m ng 3 measurements.

Figure 1 - Flow-mediated dilation of the brachial artery.

FMD was calculated as the percent change (%FMD) in brachial diameter from the resting state (100*[hyperemic diameter at selected time resting diameter]/resting diameter) for reactive hyperemia. Similarly, vasodilator response to NTG was expressed as percentage change (NTG%) in diameter between baseline and post-NTG administration.

Digital peripheral artery tonometer (EndoPAT) assessment

- Digital Pulse amplitude is measured with a Peripheral Arterial Tonometry (PAT) device by placing the probes on the tips of both index fingers (Endo-PAT 2000).
- PAT signal measurement was performed with the digital probe inflation pressure set at 10mmHg below the diastolic pressure or 70 mmHg (whichever was the lowest) as previously described in the Framingham study.
- Briefly, baseline pulse amplitude was recorded bilaterally on tips of the index fingers for 5 minutes. This was followed by vaso-occlusion on the right side (the study finger) as described above for brachial FMD.
- After 5 minutes, the cuff was rapidly deflated and the PAT signal measurement was recorded for an additional 5 minutes. As the control, measurement of non-endothelial-dependent systemic changes occurring during the study was done on the contralateral finger.



- Mean PAT amplitudes were measured 90 seconds after the occlusion for a duration of 60 seconds. Finally, the ratio of the post-to-pre occlusion PAT amplitude of the tested arm, divided by the post-to-pre occlusion ratio of the control arm, was calculated as the Reactive Hyperemia Index (RHI).
- All PAT amplitudes and RHI are automatically calculated by the EndoPAT™ with an RHI of <1.67 previously validated as the cut off to define endothelial dysfunction.

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Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events

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Aims There is growing need for the identification of novel non-invasive methodologies for the identification of individuals at risk for adverse cardiovascular (CV) events. We examined whether endothelial dysfunction, as detected by non-invasive peripheral arterial tonometry (EndoPAT), can predict late CV events.

Methods and results Reactive hyperaemia (RH) was induced following upper arm occlusion of systolic blood pressure in 270 outpatients (54 ± 12 years, 48% female). The natural logarithmic scaled RH index (L_RHI) was calculated from the ratio between the digital pulse volume during RH and at baseline. The patients were followed for CV adverse events (AE: cardiac death, myocardial infarction, revascularization or cardiac hospitalization) during a 7-year follow-up (inter-quartile range = 4.4–8). Cox models were used to estimate the association of EndoPAT results with AE adjusted for age. During the follow-up, AE occurred in 86 patients (31%). Seven-year AE rate was 48% in patients with L_RHI < 0.4 vs. 28% in those with L_RHI ≥ 0.4 ($P = 0.03$). Additional univariate predictors of AE were advancing age ($P = 0.02$) and prior coronary bypass surgery ($P = 0.01$). The traditional Framingham risk score was not higher in patients with AE. Multivariate analysis identified L_RHI < 0.4 as an independent predictor of AE ($P = 0.03$).

Conclusion A low RH signal detected by EndoPAT, consistent with endothelial dysfunction, was associated with higher AE rate during follow-up. L_RHI was an independent predictor of AE. Non-invasive assessment of peripheral vascular function may be useful for the identification of patients at risk for cardiac AEs.

Keywords Endothelial function • Outcome • Peripheral arterial tonometry • Reactive hyperaemia

Background

Coronary heart disease is the leading cause of morbidity and mortality in most industrialized societies.[1] In spite of comprehensive treatment and modification of conventional risk factors, there is still high incidence of cardiovascular (CV) events rate.[2] Thus, there is a need to identify a more individualized functional risk profile in order to personalize treatment.[3]

It has been suggested that cardiac risk factors can cause impairment of coronary vasomotor function of both the epicardial arteries and the microcirculation,[4–8] which is considered an important phase in atherogenesis.[9–11] It has been demonstrated that coronary endothelial dysfunction in humans may be associated with myocardial ischaemia.[12,13]

Coronary endothelial dysfunction is considered an early stage of atherosclerosis[14] and has been shown to be associated with an increased risk of ischaemic CV outcome events and stroke.[15–18] Assessment of coronary microcirculatory vasomotor function (especially in patients without obstructive coronary artery disease) may therefore allow the identification of patients in the early stages of coronary atherosclerosis and at risk for CV events.

However, one of the main obstacles in using peripheral endothelial function for individualized assessment of CV risk is the lack of standardization of these tests.[3,19]

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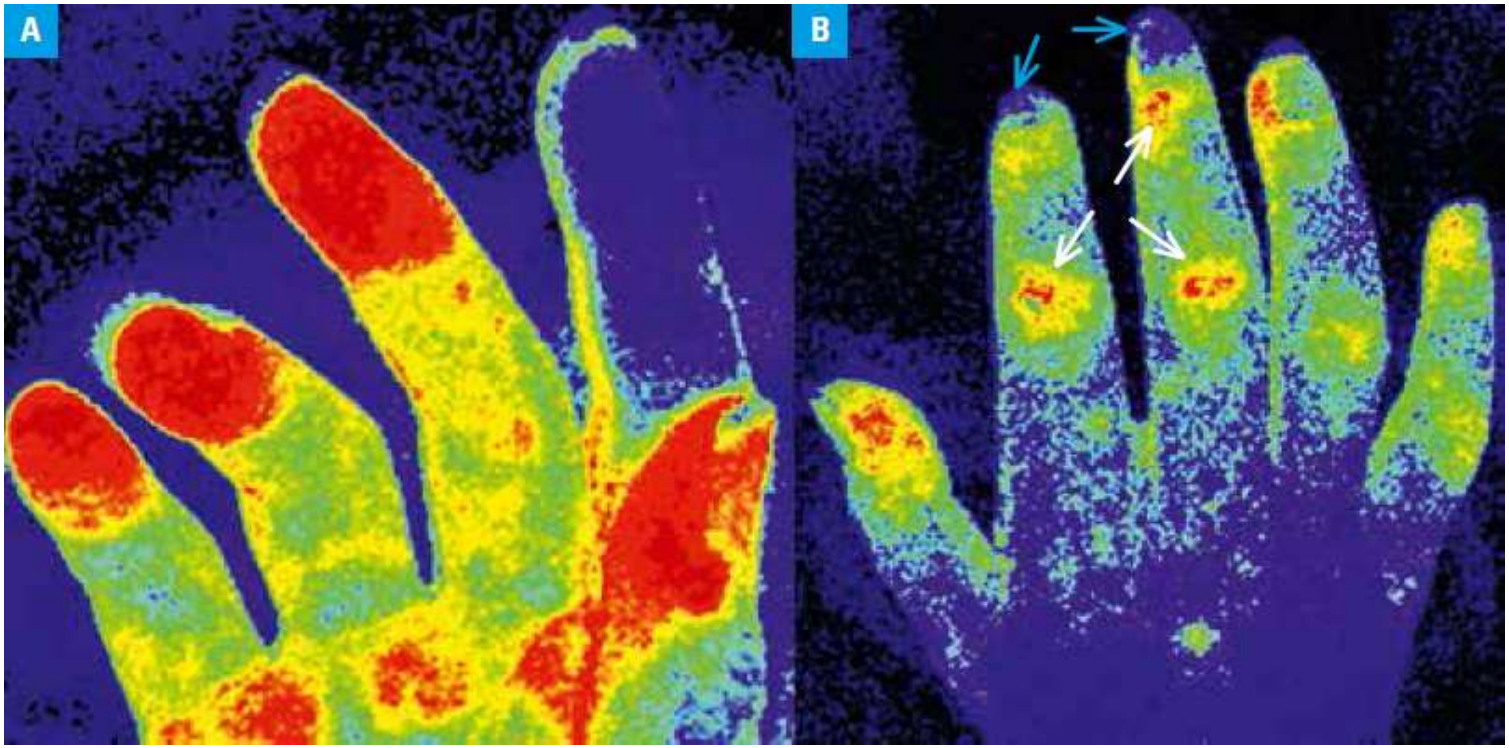
Laser speckle contrast imaging (LSCI)

- Laser speckle contrast imaging (LSCI) is a well established technique for imaging blood flow in the brain.



Laser speckle contrast imaging of Raynaud phenomenon

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Raynaud phenomenon is an episodic vasospasm of the peripheral microvessels in response to cold or stress. It can be primary, or less frequently secondary, to a systemic disease, the most frequent being scleroderma. The pathophysiology is most likely related to abnormal digital microvascular sensitivity to sympathetic stimulation that may also involve an abnormal response of the endothelium. Owing to its small size and regional heterogeneity, studies of the skin microcirculation remain challenging and the only routine method is videocapillaroscopy for evaluating microvascular structure. In addition, skin microvascular dysfunction has been described in many cardiovascular disorders.

Laser speckle contrast imaging (LSCI) is a recently developed technique that allows noninvasive, noncontact, and real-time monitoring of peripheral microcirculatory blood flow on a large area of the body.[1] LSCI is user-friendly and shows very good reproducibility as well as excellent spatial and temporal resolutions.[2] In clinical studies, LSCI coupled with reactivity tests enable to estimate the endothelial and neurovascular function.

We present the measurements of skin perfusion assessed by LSCI in patients with primary and secondary Raynaud phenomenon. FIGURE 1 shows skin flux derived from speckle contrast analysis with colors ranging from blue (no perfusion) to red (high perfusion). LSCI provides a perfusion index proportional to skin blood flow and allows to record up to 100 images per second. FIGURE 1A presents a clear lack of perfusion in the index finger in a patient with primary Raynaud phenomenon. FIGURE 1B presents the hand of a patient with scleroderma. We can see ulcers in

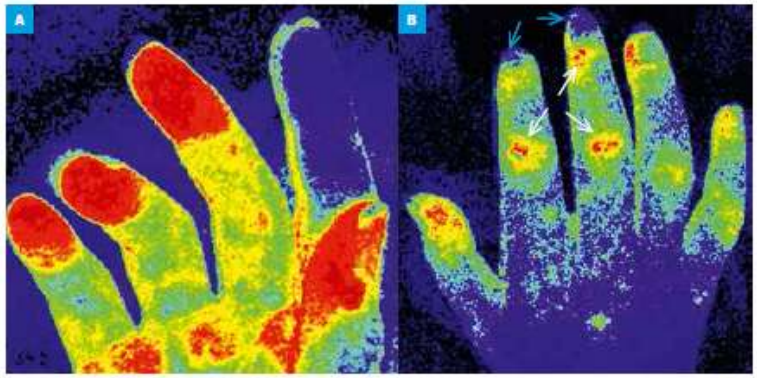

FIGURE 1 Measurement of the microvascular flux assessed by laser speckle contrast imaging: **A** – lack of perfusion in the index finger in a patient with Raynaud phenomenon, contrasting with high perfusion of the adjacent finger pads; **B** – Raynaud phenomenon secondary to systemic sclerosis: ulcers in the process of healing surrounded by an increased skin blood flow (white arrows); lack of perfusion of the last phalanges of the index and middle fingers at the site of recurrent ischemic ulcerations (blue arrows)

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Endothelial Dysfunction is Present Only in the Microvasculature and Microcirculation of Early Diffuse Systemic Sclerosis Patients

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2014 ; 32(6 0 86): S–154-60.

- ***Objective*** —To evaluate endothelial function and vascular stiffness in large, medium, small and microcirculatory blood vessels in very early diffuse systemic sclerosis (SSc).
- ***Methods*** —We studied consecutive early diffuse SSc patients, defined as < 2 years from first SSc symptom who did not have a prior cardiovascular event. Age, gender and race-matched controls were recruited. All underwent assessment of aortic pulse wave velocity (PWV), carotid intima-media thickness (IMT) brachial flow-mediated dilation (FMD), digital peripheral artery tonometer (EndoPAT) assessment and laser speckle contrast imaging (LSCI).
- ***Results*** —15 early diffuse SSc and controls were evaluated. The average age was 49 years, 63% were female and 93% were Caucasian. There were no differences in body mass index, hypertension, diabetes or hyperlipidemia between controls and SSc patients. Mean SSc disease duration was 1.3 years. In the large central vessels, there was no difference in aortic PWV (p=0.71) or carotid IMT (p=0.92) between SSc patients and controls. Similarly, there was no difference in endothelial dysfunction with brachial artery FMD after ischemia (p=0.55) and nitroglycerin administration (p=0.74). There were significantly lower values for **digital EndoPAT** measures (p=0.0001) in SSc patients. **LSCI revealed a distinct pattern** of microcirculatory abnormalities in response to ischemia in SSc patients compared to controls. Imaging demonstrated a blunted microcirculatory hyperemia of the hand with greater subsequent response to nitroglycerin.
- *Conclusions* —**These findings suggest that earliest endothelial changes occur in smaller arterioles and microvascular beds, but not in medium or macrovascular beds, in early diffuse SSc.**

All times, at diagnosis!

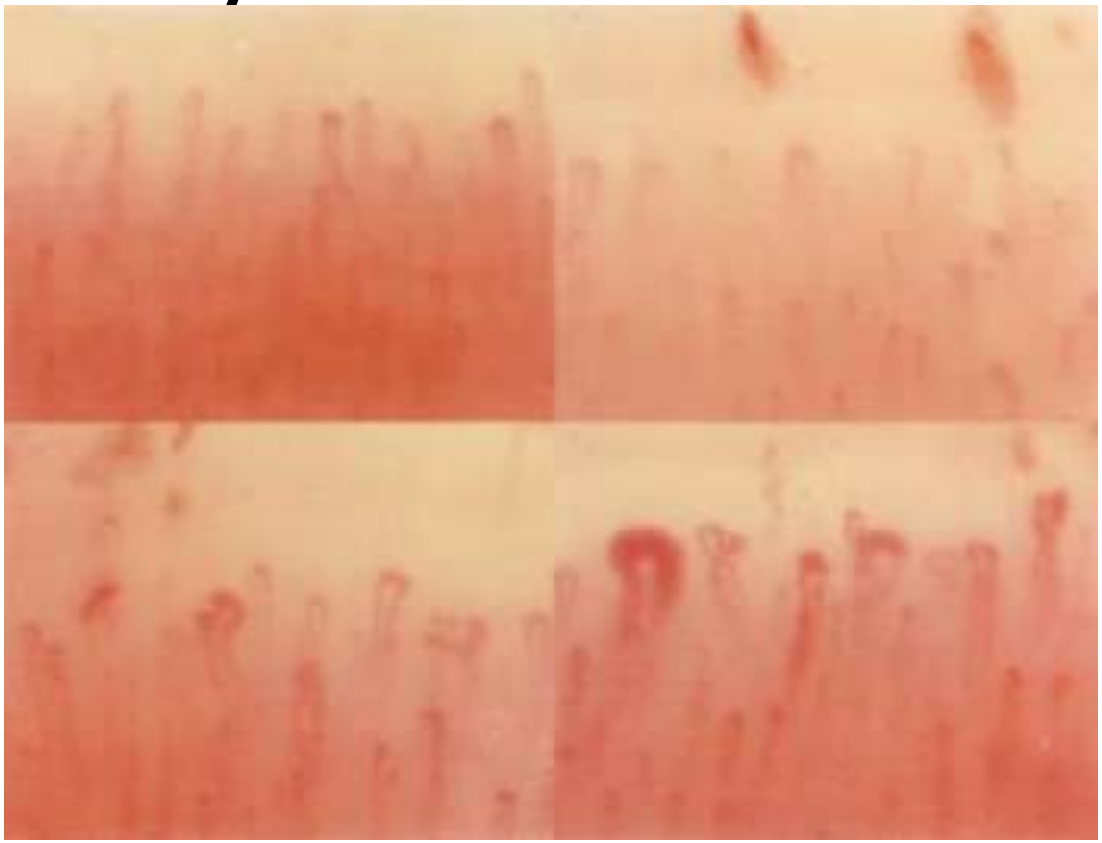
- Blood pressure;
- CV risk's factors;
- Nailfold Capillaroscopy;
- Digital Endo-PAT;
- Power Doppler ultrasonography of limbs and supra aortic with carotyd IMT;
- Echocardiography.

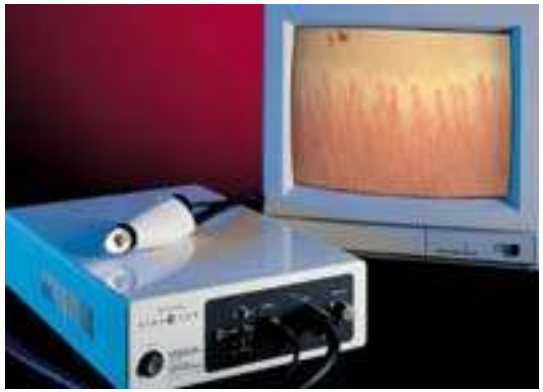
Nailfold Capillaroscopy

- is a noninvasive method to evaluate vascular dysfunction. A majority of patients with SSc have capillary dilatation associated with avascular areas and loss of normal capillary organization (1). The clinical features associated with capillaroscopic alterations and the value of nailfold capillaroscopy in predicting the presence and activity of pulmonary disease in SSc (2).

1) Maricq HR, LeRoy EC, D'Angelo WA, *et al.* Diagnostic potential of in vivo capillary microscopy in scleroderma and related disorders. Arthritis Rheum 1980; 23:183-189.
2) Bredemeier M, Xavier RM, Capobianco G, *et al.* Nailfold capillary microscopy can suggest pulmonary disease activity in systemic sclerosis. J Rheumatol 2004; 31:286-294.

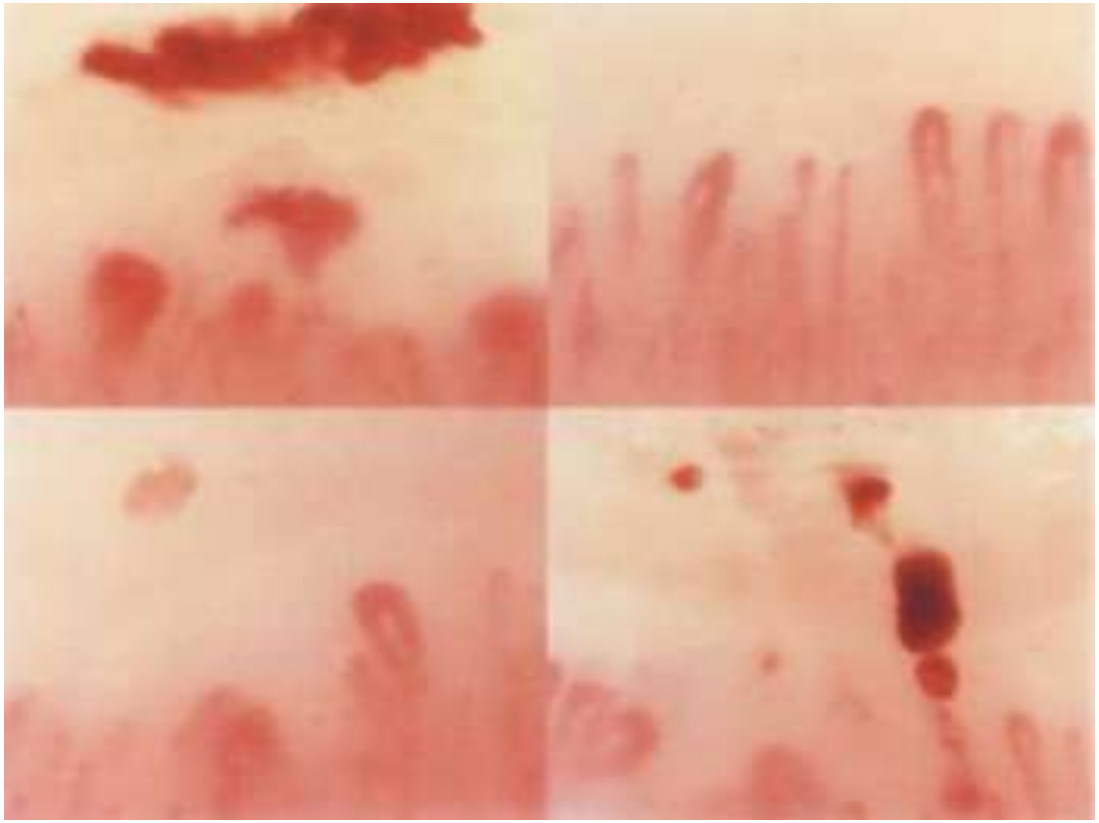
Early o Slow Scleroderma pattern

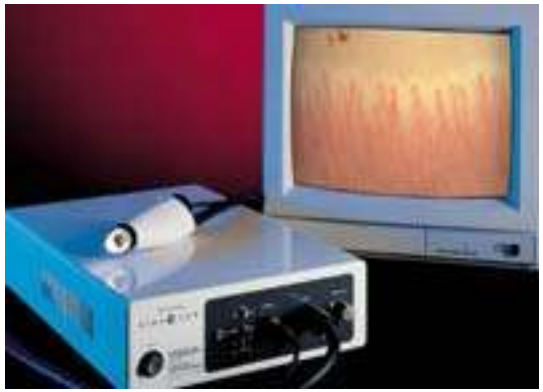




- Pettine capillare disorganizzato
- Capillari tortuosi
- Capillari ectasici
- Megacapillari
- Microemorragie

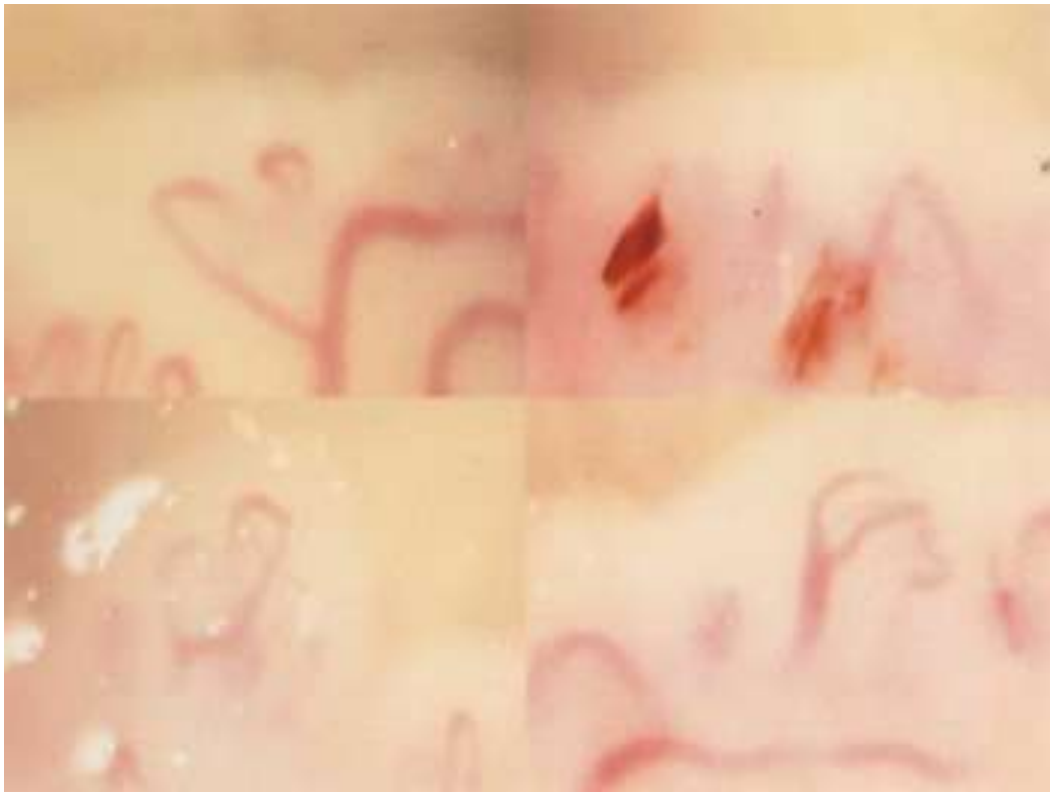
Active Scleroderma pattern

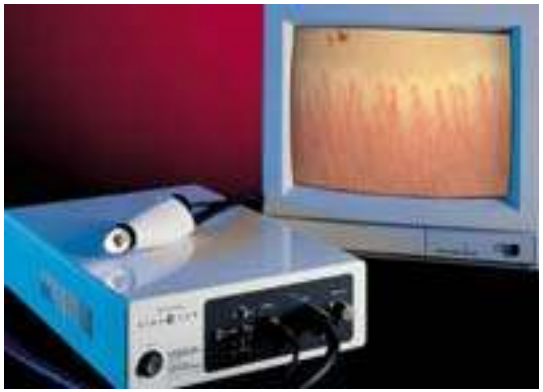




- Completa disorganizzazione del pettine capillare
- Capillari tortuosi, ectasici
- Megacapillari
- Microemorragie
- Neoangiogenesi
- Aree avascolari

Late Scleroderma pattern



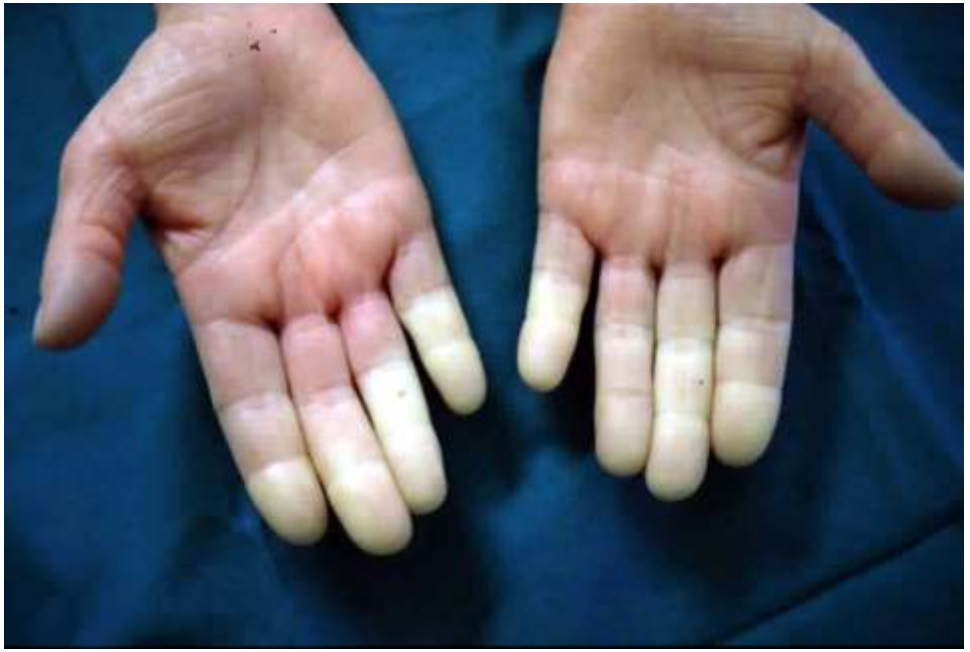


Il quadro capillaroscopico è caratterizzato dal deserto vascolare

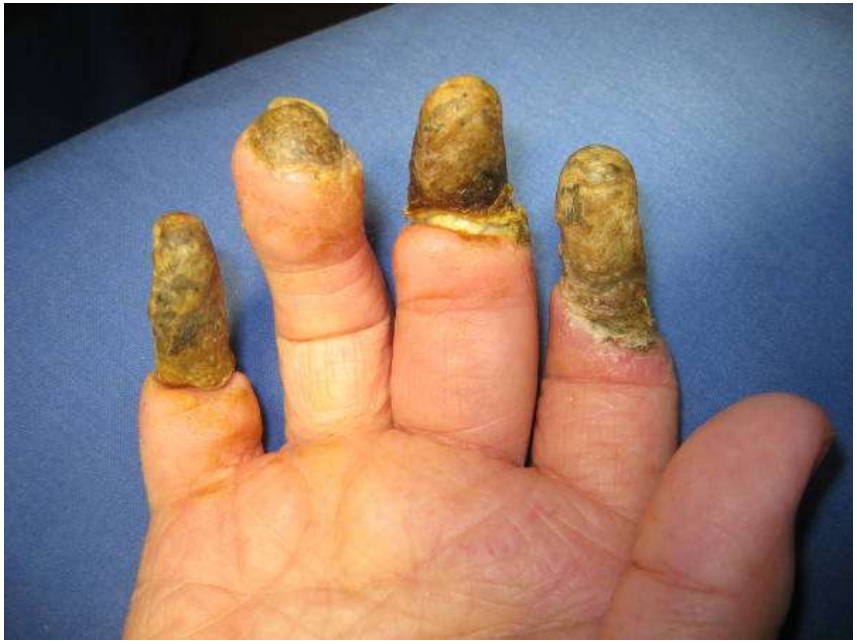
Progression of disease

Early

- Digital peripheral artery tonometer (**EndoPAT**) assessment;
- Laser speckle contrast imaging (**LSCI**).



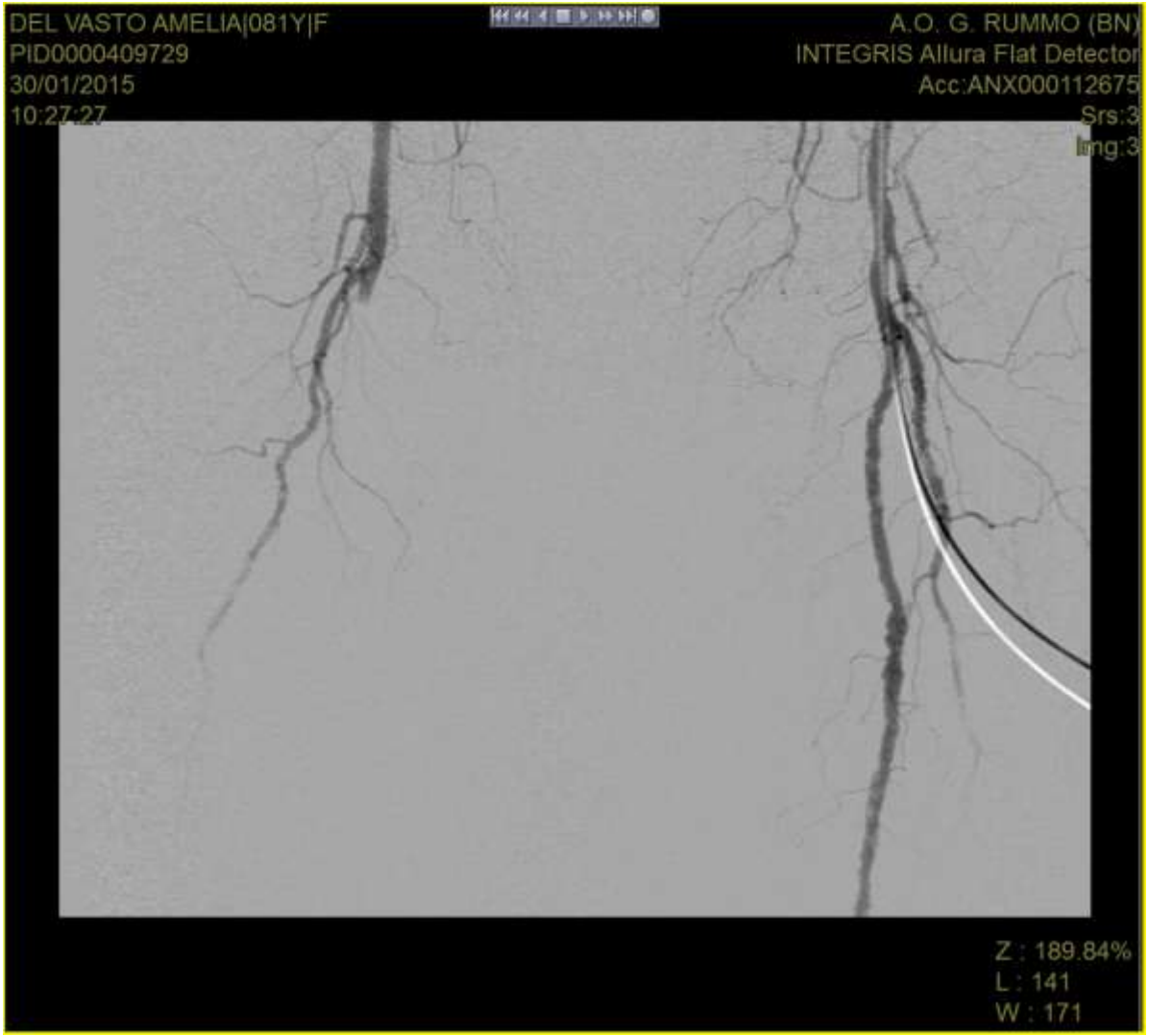
Progression of disease

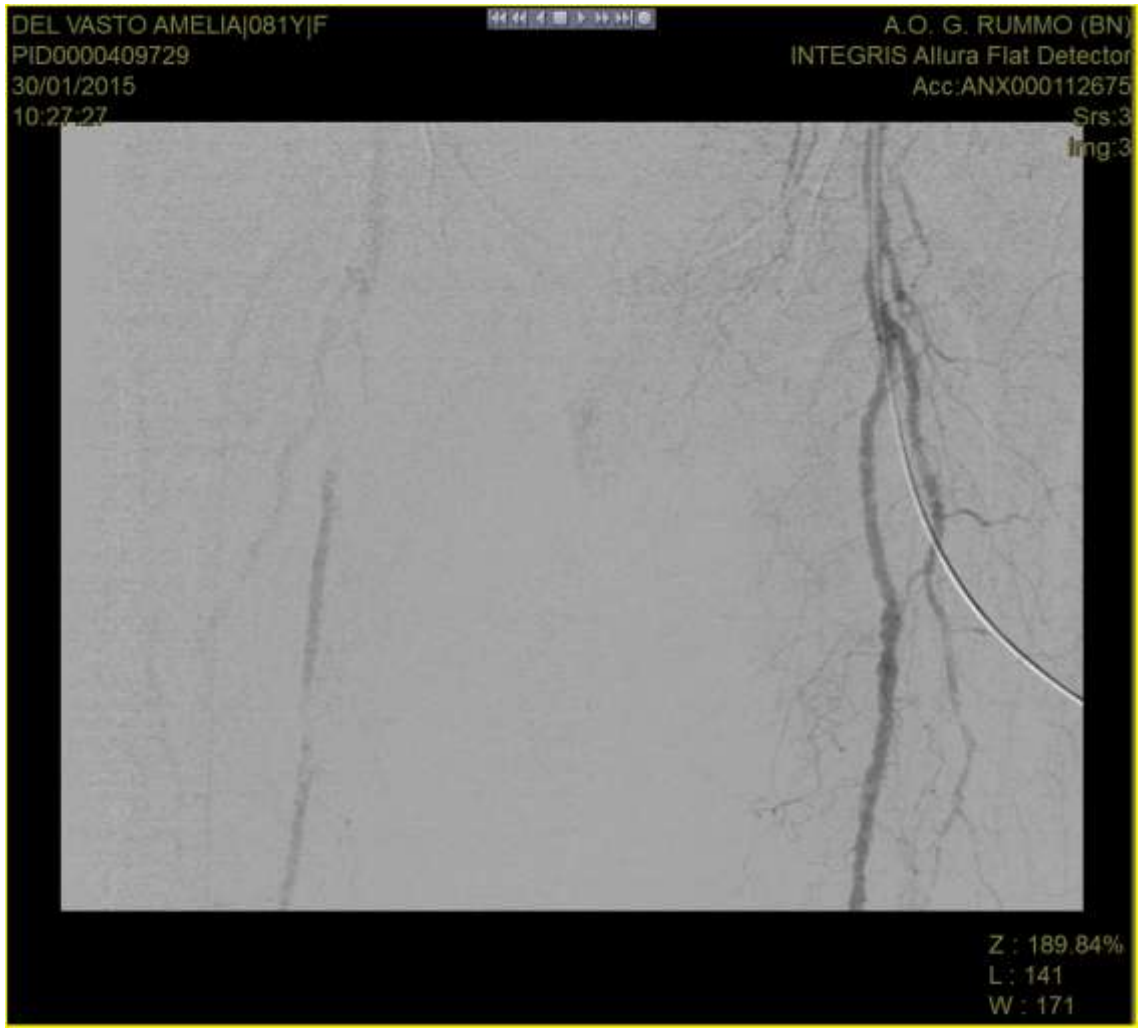


Late

- Assessment of aortic pulse wave velocity (PWV);
- Carotid intima-media thickness (IMT);
- Brachial flow-mediated dilation (FMD).

Angiography in case-report

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30/01/2015
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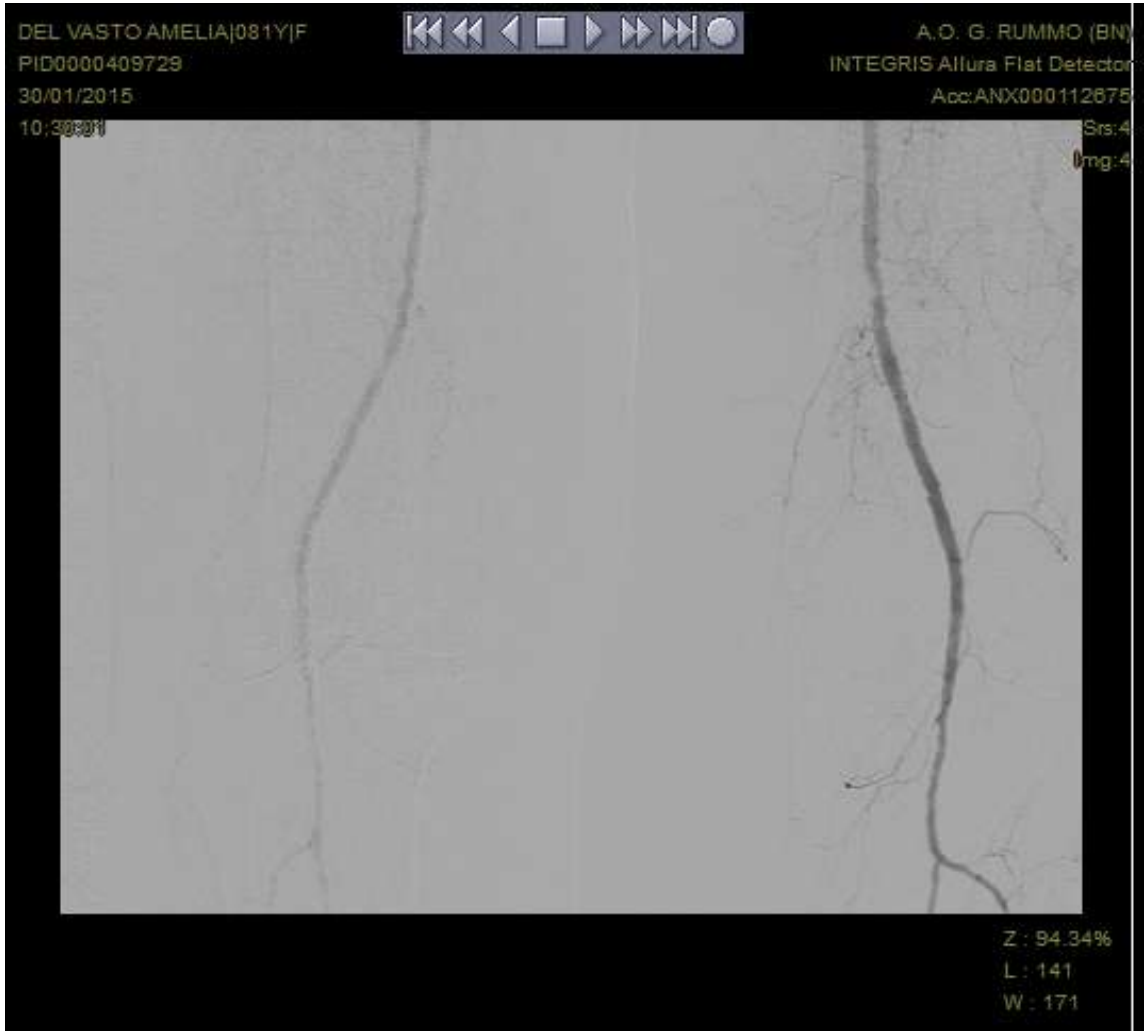
A.O. G. RUMMO (BN)
INTEGRIS Allura Flat Detector
Acc:ANX000112675
Srs:3
Img:3
Z : 189.84%
L : 141
W : 171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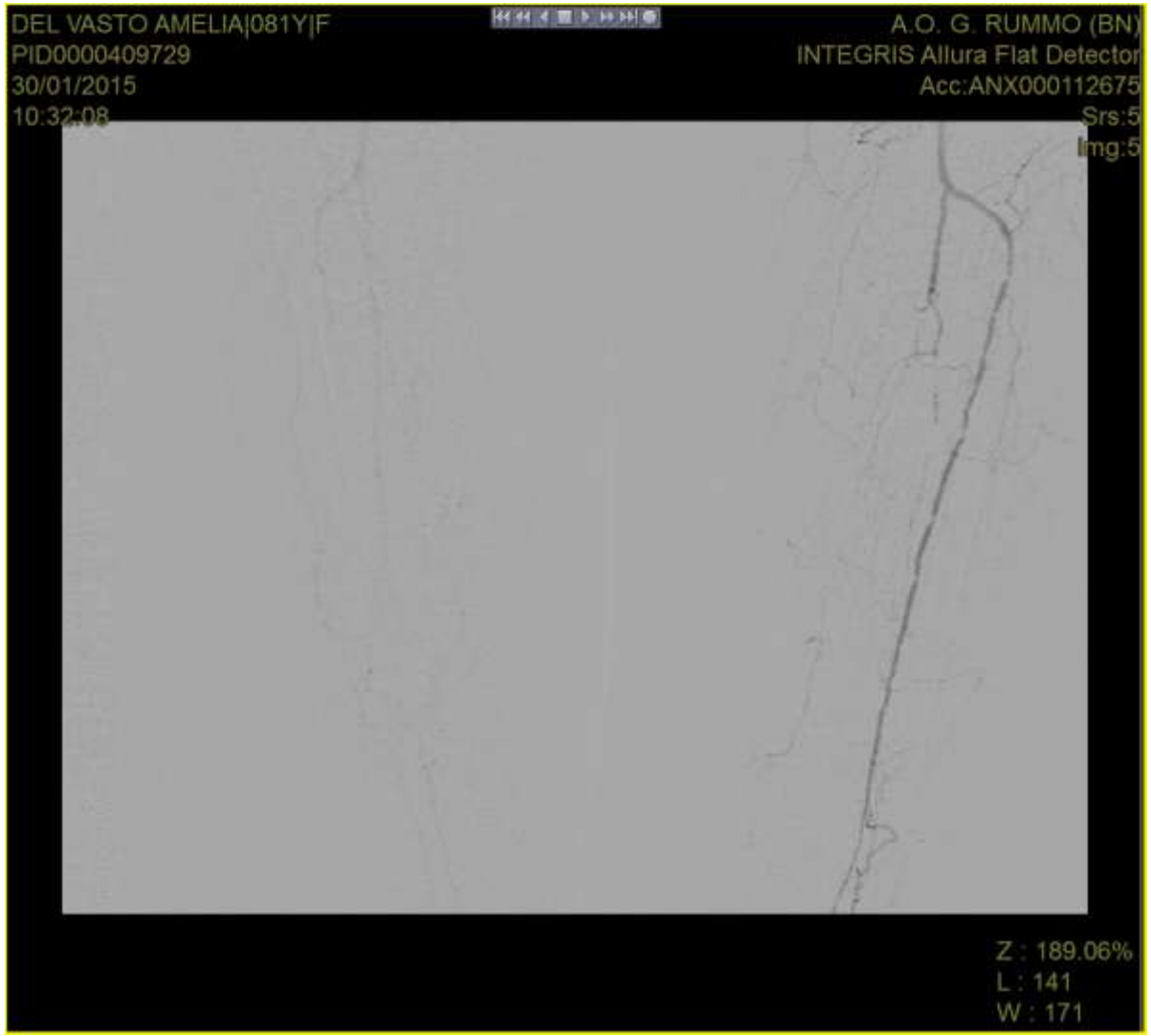
W : 171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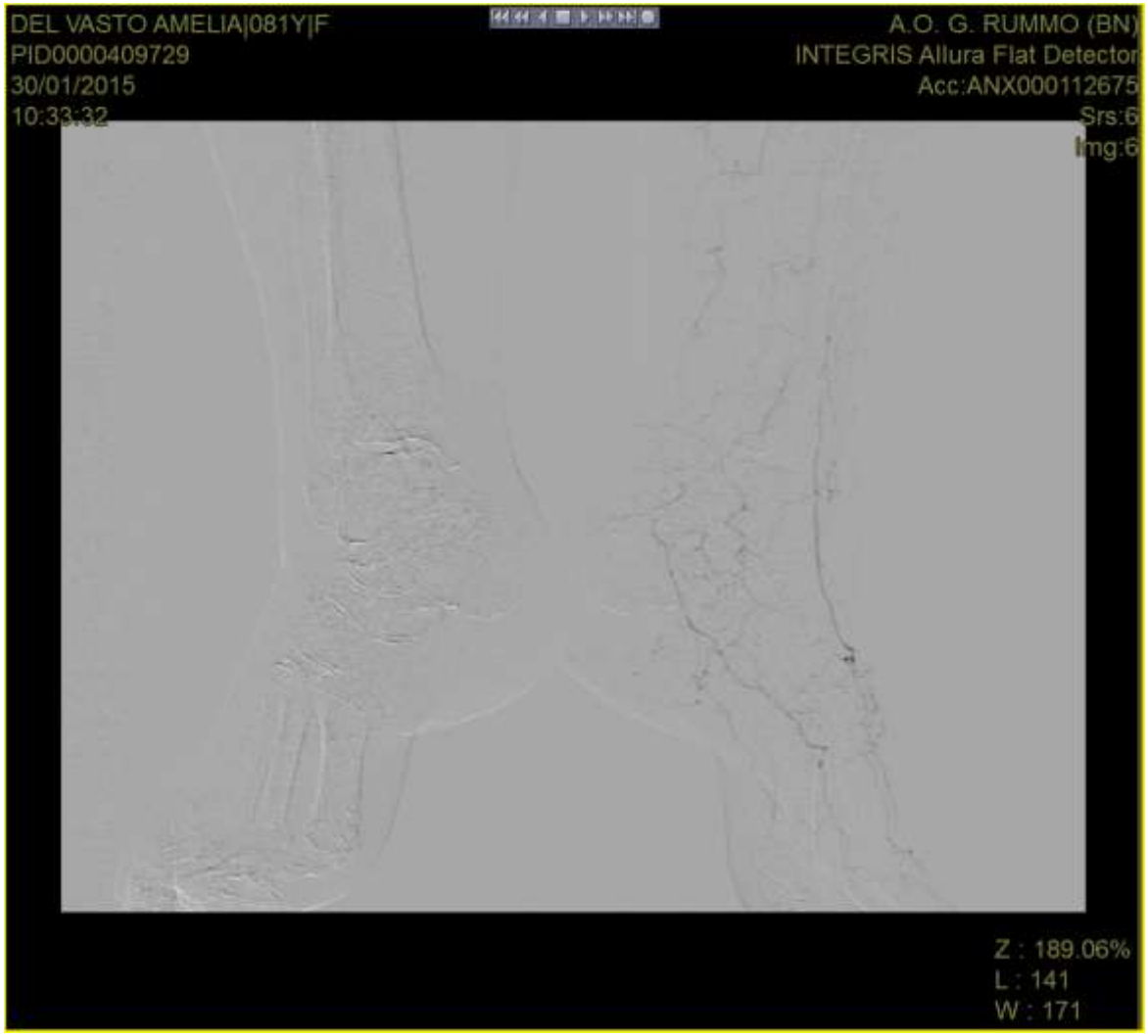
Img:5
Z : 189.06%
L : 141
W : 171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Srs:6
Img:6
Z : 189.06%
L : 141
W : 171

Take-home messages

1. E**valuate vascular involvement already in the early stages** of the disease and shared pathways in hospital between specialists.
2. Always **evaluate with arteriography doubtful cases** or not responding to treatment.
3. E**valuate the lipid profile** and immediately treat dyslipidemia with statins.
4. In the case of focal vascular stenosis, **application of stents** improves the prognosis and the quality of life.

Il contadino non sarà mai messo sotto accusa se non ottiene un buon raccolto, ma lo sarà certamente se non ha ben coltivato e ben seminato i campi.

Francesco di Sales