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Imaging techniques for assessment of vascular involvement in systemic sclerosis

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Abstract

Purpose of Review—Vascular assessment in systemic sclerosis (SSc) is included in classification criteria for this disease, thus routinely used in the evaluation of patients in which this diagnosis is being considered. In this review, imaging techniques for assessment of vascular involvement in SSc hands and skin are discussed.

Recent Findings—Longitudinal use of imaging techniques has important implications for understanding the progressive vasculopathy and fibrotic transition in SSc. Nailfold and oral capillaroscopy as well as laser speckle contrast analysis are established techniques for vascular functional assessment, but longitudinal use is challenged by equipment costs and clinical time constraints. Ultrasound techniques are well described but require technical training. Advances in mobile infrared thermography and optical coherence tomography could potentially provide a point-of-care, quantitative outcome measure in clinical trials and practice.

Summary: The equipment cost, technical training, data standardization, and invasiveness of vascular assessment techniques that quantify morphological (microangiopathy) and functional (blood flow reduction) are critical for implementation into SSc clinical trials and practice to understand progressive vasculopathy, such as wound development.

Keywords

imaging; systemic sclerosis; vasculopathy

INTRODUCTION

Systemic sclerosis (SSc) is characterized by early microvascular changes with endothelial cell dysfunction, followed by the activation of mechanisms promoting their transition into myofibroblasts with subsequent fibrosis. The complex interplay of autoimmunity, ischemia, and fibrosis in SSc involves both skin and visceral organs resulting in irreversible damage

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[1]. Endothelial dysfunction, microvascular and macrovascular damage are the hallmarks of SSc [2]. In fact, while extent of skin thickening and SSc-specific autoantibodies are recognized to have important prognostic implications and are included in the classification criteria for this disease, most classification criteria represent vasculopathy manifestations, highlighting the importance of vascular assessment [3]. Although classification criteria are not designed for diagnostic purposes, in the absence of diagnostic criteria, the classification criteria are often used to by clinicians during the work-up of patients with concern for SSc as the diagnosis [4]. Assessment of vascular involvement is similarly important for SSc patient management, as the disease is a progressive self-amplifying process, which first involves the microvascular/endothelial damage, followed by autoimmune response and inflammation, and finally fibrosis [1]. Vascular based therapeutics, even in the absence of a primary preventive action, might help in slowing disease progression and postponing the onset of major vascular events [5■,6]. There is a need for routine, cost-effective, and noninvasive imaging techniques of vascular involvement in SSc.

In SSc, correlations between morphological (microangiopathy) and functional (blood flow reduction) evaluations are established as a progressive process that results in vascular damage, insufficient repair, and ultimately loss [7,8]. Although pulmonary arterial hypertension (PAH) is diagnosed by right-sided heart catheterization according to standard definitions, there are screening algorithms to assist in diagnosis in a cost-effective manner [9],[10,11]. The fingers often first exhibit the early signs of SSc, thus, the most straightforward method for early detection is to assess the functional and structural changes through appropriate imaging technologies of the hand and skin. This review covers vascular assessment of the skin and hands in SSc to highlight the importance of developing standardized approaches.

HAND AND MOUTH VASCULAR ASSESSMENT IN SYSTEMIC SCLEROSIS

Despite broad patient-to-patient variability in SSc presentation and disease severity, Raynaud’s phenomenon (RP), a symptom complex related to digital vascular compromise in response to cold temperature or stress, is almost universally present in patients with this diagnosis [12]. Examination of the face and hands for telangiectases, as well as finger pulp assessment for pits and digital ulcerations (DU) is important for each patient, not only for diagnosis but also, for serial clinical management. The clinical disease progression of RP to DU in SSc represents micro vessel leak with hemorrhages, progressive capillary loss, and overt tissue ischemia [1]. There are several investigative tools that can be used to specifically examine vascular involvement of the hand and mouth that may reflect vascular pathogenesis in other organs.

NAILFOLD CAPILLAROSCOPY

Nailfold capillaroscopy is a safe, noninvasive tool to morphologically study the microcirculation in a patient with RP [13]. The importance of capillaroscopy is underscored by the fact that abnormal capillaries score two points of the nine required for classification of SSc [3]. As such, all clinicians diagnosing SSc must have access to capillaroscopy and a familiarity with the technique [14]. Nailfold videocapillaroscopy (NVC) is the gold standard

for assessment of peripheral microvascular morphology and thus allows classification and scoring of capillary abnormalities with respect to different microangiopathy patterns (early, active, and late) at the nailfold level [15]. Early phase microangiopathy is characterized by well preserved capillary architecture with a few dilated capillaries and microhemorrhages. The active pattern typically demonstrates mildly disorganized capillary architecture with many dilated capillaries and microhemorrhages along with avascular areas. The late pattern shows severely disorganized capillary architecture with dilated capillaries and microhemorrhages, but more significantly, a marked reduction in the number of capillary loops with large avascular areas. Even with limited training and experience, agreement for the identification of active and late patterns is achievable [16]. The late pattern on NVC is an independent predictor of DU in SSc [17]. Unfortunately, access to and training in NVC is not readily available in some countries, where this procedure is not reimbursable and due to the time it takes, is not feasible for serial use in clinical care [18].

Capillary assessment by dermatoscopy (used synonymously with the term dermoscopy) due to its low cost, quick acquisition of images and more frequent use amongst non-SSc specialists, is a valid clinical tool for nailfold assessment in a patient with RP [19]. There are a few important aspects to documentation when using a dermatoscope, including documentation of the magnification used, which typical ranges from 10× to 30×, and the attachment of a device to allow photo documentation. While dermatoscopy does not provide the detailed assessment that is given by NVC, it can successfully identify the nailfold SSc-pattern as well as identify nonspecific abnormalities that can subsequently referred for NVC available in subspecialty centers that care for SSc-spectrum diseases [20].

The procedure for dermatoscopy is like NVC. Each subject should be acclimatized to the exam room for a minimum of 15 min before the nailfold is examined at room temperature of about 21–22°C. Like NVC, a thin layer of oil is applied to the nailfold of the second to fifth digit on both hands to enhance sharpness of images. However, unlike NVC the dermatoscopy is not placed directly on the nailfold. The distance of the dermatoscope from the nailfold is determined by image sharpness that is influenced by either the steady hand of the operator, or a platform that can fix the device, since clear images require no movement. The automated focusing system of a dermatoscope results in the possibility of slight variation in magnification, and in general, provides a single, wide view image.

Nailfold capillaroscopy plays a significant role in the diagnosis of systemic sclerosis, as microvascular damage is an early marker of disease. It is also useful to assess the severity of disease. Structural abnormalities, such as devascularization areas and distortion of the capillary bed architecture, characteristic of the late microvascular damage, are strong predictors of the occurrence of DU in this population of patients. Abnormal nailfold capillaroscopy findings are associated with the presence of pulmonary arterial hypertension (PAH) in patients with SSc and correlated with PAH severity [21]. However, there is no consensus on its role in the follow-up of SSc patients [20]. Training of healthcare providers assessing RP, especially fellows and rheumatologists, in this technique is an important unmet need in SSc [18].

ORAL CAPILLAROSCOPY

Oral regions of the mouth can be examined by microscopy in a noninvasive method that assesses microcirculation. Oral capillaroscopy is performed with a sterile probe cap and can be applied to incisor, buccal and sublingual regions. One study of 20 SSc patients, and 20 age- and sex-matched controls using a portable videocapillary CapiScope (KK Technology) with a Sidestream Dark Field (SDF) camera demonstrated decreased oral vasculature in SSc patients [22]. Green light emitting diodes (from the SDF camera) is absorbed by hemoglobin in RBC, which allows RBC visualization in contrast to the vascular background that allows indirect measurement of the glycocalyx layer in sublingual capillaries. A study of 26 subjects (16 SSc patients and 10 healthy controls) reported that sublingual microcirculation and glycocalyx are impaired and that SDF imaging findings correlate with those of NVC [8]. Another study of sublingual capillaroscopy in 39 SSc patients, found a significant correlation between intravital microscopy of the sublingual microcirculation and NVC in terms of sublingual total microvascular density and microangiopathy evolution score, which includes the sum of three scores for loss of capillaries, disorganization of the microvascular array, and capillary ramifications [23■]. Serial use of a noninvasive and automated sublingual microvascular function testing and glycocalyx measurement in the clinical setting is needed to best understand the implication of these findings.

LASER TECHNIQUES

Capillaroscopy and laser Doppler techniques can be used together to complement each other in morphologic and functional evaluation of microcirculation. Laser Doppler techniques assess the skin capillary perfusion by measuring the Doppler shift induced by laser light scattering of moving red blood cells whereas laser speckle contrast imaging (LSCI) measures the fluctuating granular pattern produced by laser light reflected on moving red blood cells. Laser Doppler Flowmetry (LDF) has excellent speed, but poor reproducibility, requires skin contact, and due to single point measurement, has high spatial variability. Laser Doppler imaging (LDI) has good reproducibility but is slow at capturing changes in cutaneous perfusion and thus, not good at recording rapid changes in perfusion. LSCI is faster at capturing changes in cutaneous perfusion but is not good for assessing areas of low perfusion. Studies comparing laser Doppler techniques and conventional NVC showed that cutaneous perfusion measured by LDF correlated well with NVC findings [24■■]. More studies are needed for validation of LSCI in SSc.

Although the validated method to study the morphological vascular alteration in SSc patients is NVC, laser speckle contrast analysis (LASCA) is helpful in the evaluation of functional damage of microvascular system [24■■]. LASCA is a safe, noncontact, noninvasive microvascular imaging modality that is a less time-consuming technique compared to NVC and can be used to quantify peripheral blood perfusion in the cutaneous microcirculation over large skin areas. LASCA used alone or together with reactivity tests, is useful for the monitoring of disease progression, response to treatment and DU outcome [24■■]. LASCA is a credible instrument in patients of Black ethnicity with SSc [25]. LDF at the single fingertip level correlates with LASCA, but LASCA has a lower intra-operator variability than LDF, can evaluate larger skin areas, is significantly less time consuming and

more readily accepted by patients [24■■]. Although LSCI is like LASCA, the contrast is calculated on a single pixel over several time frames. LSCI has a spatial resolution which is five-times larger than that of LASCA, but it has a poor temporal resolution. LSCI of the hand demonstrates lower perfusion in SSc patients than healthy controls and directly correlated with the NVC findings [26,27]. There is a good correlation between peri-oral and lip LSCI to mouth-opening in SSc patients, but no significant difference was observed between SSc and healthy subjects at the peri-oral area [28].

INFRARED THERMOGRAPHY

Infrared thermography (IRT) indirectly measures the cutaneous thermoregulation process to produce an image according to the temperatures emitted by the human body and can be obtained using portable digital thermal cameras attached to a mobile phone, known as mobile thermography [29]. There is good correlation between LSCI and IRT for the assessment of digital perfusion [30]. IRT is an effective tool for assessing patients with rheumatic disease, but protocols require recording acclimatization time, distance between the camera and the individual, temperature, and ambient humidity [31■■]. IRT assessment of SSc hands is often combined with a local cold challenge to allow dynamic vascular assessment under conditions thought to simulate those responsible for an attack of RP. A local cold challenge does not account for the influence of convective and conductive heat exchange on surface skin temperature, thus does not truly recapitulate RP [32]. Although IRT measurements correlate only moderately with density of capillaries, abnormal initial thermography associates with nailfold capillaroscopy patterns and identifies SSc that are more likely to develop digital ulcers and require more frequent surgical debridement [33,34]. Of interest, baseline thermographic temperature is influenced by gender but, not race and trends show decreased perfusion in tobacco users relative to nonsmokers, which highlights the importance of subject characterization [35]. Additionally, while not specifically studied in SSc, lower facial skin and submental triangle region temperatures, measured by IRT, can help identify patients with obstructive sleep apnea [36]. Though IRT devices are valuable for assessing skin circulation, they require prospective clinical studies to determine the validity, reliability, sensitivity, and specificity of these measurements for routine use in patients who are at risk for vascular disease and wound development [37].

IMAGING OF CALCINOSIS

Radiography, high-frequency ultrasound (HUS), computed tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI) can be used to quantify the vascular complication of calcinosis [38,39■]. Radiographs and HUS are the least expensive options for following calcinosis lesions. Radiographs allow rating of calcinosis and a description of the morphological pattern, such as nodular, sheet-like, reticular, amorphous, and linear [40]. By HUS, which is a low-cost, point of care, nonionizing imaging modality, calcinosis is described as hyperechoic foci with or without acoustic shadowing, which may increase detection, but may be more time intensive and is dependent on sonographer experience with less reproducibility [39■]. The addition of Doppler imaging modes can result in artifact [41]. Nonetheless, HUS is helpful for following cutaneous ulcers in SSc [42].

Whole-body fluorine-18 fluorodeoxyglucose PET/CT can identify widespread soft-tissue calcinosis characterized by elevated glucose uptake in SSc [43]. Without the PET component, traditional CT can provide information regarding adjacent anatomic structures, which can guide a surgical approach to management [44]. Novel CT approaches, such as 3D visualization and dual-energy, provide better visualization, but are limited for serial use by cost and radiation exposure [39■]. MRI with high contrast resolution and multiplanar imaging effectively evaluates soft tissue pathology without associated radiation exposure, but cost limits feasibility. Furthermore, conventional MRI sequences may not be able to identify small foci of calcinosis, but the addition of gradient-echo imaging can improve detection [45].

ANGIOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY

Vascular lesions of the hand are unique and more difficult to image because of the terminal vascular network, thus, to guarantee a high-quality exam the hand should be evaluated independently and not as part of an upper limb protocol [46■■]. Conventional angiography is the gold standard for vascular abnormalities. CT angiography (CTA) is performed with two successive acquisitions after the injection of iodinated contrast media. There are advanced CT imaging techniques such as dynamic CTA and super high-resolution (SHR)-CTA, which allow a clear visualization of the most distal arteries [46■■]. Dynamic contrast-enhanced magnetic resonance angiography (MRA) yields comparable information to conventional angiography about vascular anatomy, stenosis, obstruction, and vessel inflammation. Tissue characteristics influence MRI signal intensity, which can be manipulated pharmacologically for the purpose of contrast enhancement through altering the relaxation time of the tissue [47]. MRA is usually based on the administration of a gadolinium-based contrast agent and time-resolved sequences. Image contrast is the difference in brightness between an area of interest and the surroundings such that the larger the difference in brightness between different tissue types, the easier it usually is to differentiate them from each other. Contrast-enhanced T1-weighted fat-suppressed sequences provide a means to evaluate thickening and enhancement of the arterial wall. MRA of the hand can help rule out vasculitis mimics but is usually not indicated if drug or chemical related, frostbite, or vaso-occlusive disease is suspected [46■■].

Optical coherence tomography angiography (OCT-A) is method to directly visualize capillary-level vascular and structural features within skin *in vivo*, which has the potential to provide new insights into the pathophysiology, as well as dynamic changes of SSc skin [48]. OCT-A visualizes vasculatures from two separate layers of skin, the small capillaries of the superficial papillary dermis and the larger vessels of the deeper reticular dermis [49]. OCT-A imaging of the nailfold correlates with microvascular injury classically described by NVC [49]. The development of dynamic OCT is proposed a standardized imaging technique that could potentially provide a quantitative outcome measure in clinical trials and practice [50■■].

VASCULAR FUNCTIONAL STUDIES WITH PERIPHERAL ARTERIAL TONOMETRY, DIGITAL THERMAL MONITORING, FLOW MEDIATED DILATION, AND AUTONOMIC NERVOUS SYSTEM INVESTIGATIVE TOOLS

The peripheral arterial tonometry (PAT) technique that measures arterial pulse volume changes in the finger as a result of vasomotion (vasoconstriction and vasodilatation) identified early endothelial changes in smaller arterioles and microvascular beds in early diffuse SSc [51]. The PAT technique compares pulse amplitude at the fingertips before and after a 5-min arm-cuff-induced reactive hyperemia. However, the PAT probe includes a fingertip cuff that obstructs microvasculature at the point of measurement; therefore, may not be able to accurately evaluate microvascular reactivity at the fingertip. Like the PAT technique, digital thermal monitoring (DTM) is performed during a 5-min arm-cuff-induced occlusion to induce reactive hyperemia and indirectly measures endothelial function, perfusion, and vasodilator ability. Both DTM and PAT are automated, but DTM of vascular reactivity assesses Doppler ultrasound hyperemic, low frequency, blood velocity of radial artery and a fingertip vascular function without fingertip occlusion. The DTM method measures both cutaneous microvascular and vascular reactivity that result in increased blood flow to the fingers because of reactive hyperemia. A single center study of 34 SSc subjects identified that DTM correlated to flow mediated dilatation (FMD), which is a test of endothelial function in the brachial artery [52].

FMD in SSc has identified that endothelial dysfunction seems to be primarily present in microvasculature [53]. When FMD is combined with endothelium-independent, nitroglycerin-mediated dilatation (NMD), FMD is impaired prior to NMD in SSc, suggesting assessment of FMD in the preatherosclerotic stage may have a beneficial diagnostic, prognostic, and therapeutic relevance [54]. FMD is reported as an independent predictor of DU [17]. FMD can be combined with carotid ultrasound to measure carotid intima-media thickness (CIMT) and carotid atheroma plaques (AP) in order to detect accelerated atherosclerosis or macrovascular disease. CIMT is reported at older ages and after longer disease duration in SSc [54]. Macrovascular disease is more common among SSc with diastolic dysfunction of the left ventricle on echocardiogram [55■]. A study of 70 SSc patients identified that glucocorticoids may be associated with an early vascular damage in these patients detected by FMD and carotid ultrasound [56]. This highlights the value of serial vascular assessment in SSc.

Autonomic nervous system (ANS) involvement, consisting of parasympathetic under activity and sympathetic overdrive, is regularly described in SSc [57]. Increased heart rate, diminished heart rate, and blood pressure variability are the most reported alteration [57]. Gastrointestinal involvement is reported to correlate to ANS involvement [58]. Quantitative sudomotor axon reflex test (QSART) is designed to stimulate the autonomic nervous system and evaluate how nerves that regulate sweat glands responds to stimulation. A SSc QSART protocol for skin symptoms (digital ulcers, pernio-like eruptions, subcutaneous calcifications, telangiectasia, nailfold capillary dilatation/bleeding and degree of skin sclerosis) and skin surface temperature is under investigation in Japan for a observational clinical study [59]. This study adopts two evaluation points, summer and winter, to observe

effects of temperature on sweating. The interaction of vascular and neurological symptoms are captured in this functional study.

Irrespective of PAT, DTM, FMD, or QSART studies, it is important to highlight that mean blood pressure (BP) is an important determinant of arterial stiffness in SSc [60]. Tobacco cessation and BP monitoring is mandatory for SSc patients for both detection of scleroderma renal crisis (SRC) and cardiovascular risk reduction [61]. Thus, while exciting advances in the field will help inform SSc vasculopathy progression, perhaps the most important routine, cost-effective, and noninvasive imaging technique for vascular involvement in SSc is home BP monitoring.

CONCLUSION

Vascular assessment of the skin and hands in SSc ideally captures the natural history of vasculopathy and fibrotic transition in a cost-effective methodology that captures quantifiable parameters of disease activity and damage with minimal training requirements (Table 1) [62]. Although nailfold capillaroscopy has a critical role in diagnosis, practical applications for serial monitoring are limited by standardization, training, and time-constraints. Costs of imaging are an important consideration for advances in CT, MRI, and PET as applied to longitudinal characterization of vasculopathy. Techniques including automated oral capillaroscopy, PAT, DTM, FMD, IRT, and OCT require prospective clinical studies to determine the validity, reliability, sensitivity, and specificity of these measurements for routine use in SSc patients who are at risk for vasculopathy progression. Nonetheless, the importance of collaborative efforts to standardize assessment of SSc disease progression is critical for longitudinal vascular assessment of the skin and hands to inform discovery [63]. Serial vascular assessment remains at the forefront of critical unmet needs for SSc.

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KEY POINTS

- Clinical vascular assessment is critical for systemic sclerosis patient care and clinical trials.
- Nailfold and oral capillaroscopy, thermography, and laser speckled contrast analysis are useful tools for vascular assessment.
- Techniques such as mobile thermography and optical coherence tomography are promising but require prospective clinical studies to determine the validity, reliability, sensitivity, and specificity of these measurements for routine use in systemic sclerosis patients who are at risk for vasculopathy progression.

Table 1.

Noninvasive vascular methods

Noninvasive vascular method	Vascular data provided	Principle strength	Main weakness
Nailfold capillaroscopy	Morphological	Standardized protocol	Trained operator
Sublingual capillaroscopy	Functional	Automated	Availability
Laser speckle contrast imaging (LSCI)	Functional	Noncontact	Inadequate in low perfusion
Laser speckle contrast analysis (LASCA)	Functional	Intra-operator variability	Spatial resolution
Infrared thermography	Functional	Specific for skin circulation	Detailed protocol
Calcinosis assessment • Ultrasound (US) • CT • MRI • PET	Morphological	 • US: cost • CT/MRI: preoperative anatomic information • PET: widespread evaluation	 • US: trained operator • CT: radiation • MRI: misses small foci • PET: cost
Optical coherence tomography angiography (OCT-A)	Morphological	Quantitative in two layers of skin	Validation in SSc
Peripheral arterial tonometry (PAT)	Functional	Automated	Fingertip occlusion
Digital thermal monitoring (DTM)	Functional	Automated	Requires adequate baseline temperature
Flow mediated dilatation (FMD)	Functional	Standardized protocol	Trained operator
Quantitative sudomotor axon reflex test (QSART)	Functional	Captures neurologic skin symptoms	Trained operator