ABSTRACT

Our objective was to identify a core set of variables for the assessment of vascular involvement in scleroderma that is simple, reproducible, and reflects the presence of vascular disease in SSc. To do so we carried out an extensive literature review of published studies relating to the assessment of vascular involvement in SSc, i.e. studies dealing with clinical parameters, functional vascular studies, cold presser testing, nailfold capillary microscopy and circulating vascular markers.

After extensive review of published studies and critical assessment of proposed vascular parameters, the subcommittee endorsed what it considers to be the minimal requirements for the documentation of vascular involvement in SSc. The core set variables include two parameters: Raynaud’s phenomenon and digital ulcers. This set is simple, reproducible and should be included in the assessment of SSc patients in clinical investigational studies. The subcommittee also however recognizes that there exists a promising set of vascular variable that still needs further investigation.

Possible vascular parameters

I. Raynaud’s phenomenon

Patients with Raynaud’s complain of cold hands and feet in association with color change in the digits. The symptoms appear suddenly as attacks that are triggered by exposure to cold temperature or emotional stress. Closure of blood vessels causes skin pallor that is followed by cyanosis in association with numbness and pain. Reversal of the vasospastic attacks occurs generally 10-15 minutes later in association with return of normal color or a “blushed” or mottled appearance of the skin.

Attacks of RP are traditionally assessed by their frequency, number of involved digits, symmetry, severity of symptoms and degree of associated pain. This information is best recorded in a diary kept by the patient. Some studies have used color-coded photographs depicting characteristic and uncharacteristic features of RP to verify true RP attacks (1). However, the additional information gained by this method is marginal and does not warrant the effort involved. The attack rate is defined as the number of attacks divided by the number of observation days. Attack severity is usually rated on a numerical scale (1: mild, 2: moderate, 3: severe, and 4: very severe). Associated pain is usually assessed using the Short Form Health Survey (SF-36) or the Visual Analog Scale (VAS, 0-10 scale). Raynaud’s Condition Score (RCS) is a recently introduced tool that combines the num-
ber and duration of attacks with VAS assessment of severity (2).

II. Digital ischemia
Digital vascular occlusion is assessed by the presence of small areas of fingertip ischemic necrosis or ulceration that often leaves pitted scars. Gangrene of the terminal portions of the phalanges may occur in some patients. Painful ulcerations are sometime seen at sites of flexion contractures (proximal interphalangeal joints). Loss of digital pads (atrophy), digital scars (pitting), and digital amputation should be recorded and quantified.

III. Telangiectasias
Telangiectasias are frequently seen in the limited form of SSc. They are defined as dilated small blood vessels visible to the unaided eye, and usually represent dilated capillaries or venules. Telangiectasias generally involve the fingers, palms, lips, tongue, face and mucous membranes.

IV. Functional vascular studies
Numerous non-invasive methods are used to investigate vascular function in SSc. Most of the reported techniques are not standardized, validated or uniformly adapted by investigators, however. Many published studies have examined a small number of patients and frequently the clinical composition of the patients is not given in detail. Thus, patients with primary RP are often mixed with SSc patients, leading to potential loss of clinical significance for both. It must be said that some techniques have no clear or direct clinical relevance. Furthermore, the reproducibility of results is rarely examined. Improved circulatory performance after repeated cold stress was reported in one of the few studies that investigated the reproducibility of non-invasive vascular studies in SSc (3), suggesting the presence of an adaptation phenomenon that should be considered in clinical studies. Hence, the addition of a placebo (control) group is essential in any clinical trial and baseline data should not be used as control values. Reported non-invasive vascular studies include the following:

1. Ultrasound-based techniques for the assessment of blood flow, including color laser Doppler ultrasound measurements of blood flow, velocity, wave-form, wall-lumen ratio and digital pressure. The current maximum resolution of color laser Doppler ultrasound is about 0.5 mm in the blood vessel diameter. Thus, this technique is suitable for the evaluation of flow velocities, digital perfusion, the flow pattern in the palmar and digital arteries, and the deep radial arch at rest and after cold challenge. However, distinguishing patent from occluded vessels requires the use of a vasodilator to exclude vascular spasm, an often-neglected strategy. Other variations include more complicated assessments, such as determining resistance and pulsatility indices and peak systolic velocity. Published studies suggest that all parameters are significantly lower in primary and secondary RP patients when compared to normal control subjects; however, no clear difference is usually seen between the two forms of RP (4-10).

2. Provocative tests that examine enhanced vasospasm or defective vascular dilatory potential in SSc:
   - Cold challenge: This test is applied by local hand cold exposure or by total body cooling using a cooling blanket, or preferably, in an environmentally controlled room using a wide range of cooling temperatures from 4°C up to 10°C for variable intervals. In the simplest test, the hands are placed in ice water or a cold air box for a variable amount of time. Circulatory adequacy is evaluated by examining skin temperature, digital pressure and by flow studies. This test has considerable variation and does not distinguish primary from secondary RP. Other tests involve circulating cold water around the middle region of the phalanges after arresting the blood flow using an inflated digital pressure cuff placed proximally for 5 minutes. Digital pressure is then recorded as the reopening pressure after occlusion and cooling are stopped. Other tests involve a gradual reduction in water temperature with simultaneous recording of the flow and pressure to define the temperature that causes 0 flow and/or 0 pressure (critical closing phenomenon). These are reliable tests and are in general better than those that record skin temperature and blood flow alone, since the latter are different in different fingers, are affected by emotion, pain, and food intake, and fluctuate throughout the day (11, 12).

   - Assessment of vasodilatory capacity: Measurement of hyperemia after heating (local or total body, up to 43°C) by laser Doppler flow can separate control subjects from patients with primary or secondary RP. In SSc, maximal vasodilatation during heating is inversely related to the number of involved organs. The reactive post-occlusive hyperemic response is another approach to studying the same phenomenon. Here the flow is measured following 5 minutes of supra-systolic proximal occlusion of blood flow. Patients with primary RP perform similarly to control subjects, while SSc patients routinely demonstrate reduced flow at baseline and at peak flow. Using 3 minutes of occlusion is reported to result in reduced flow that is associated with decreased cutaneous O2 (hyperemic hypoxia). These tests have an excellent clinical potential, but insufficient experience and lack of standardization distinctly limit their usefulness (13-15).

V. Digital blood pressure
Digital blood pressure as judged by strain-gauge plethysmography or Doppler can measure the duration of RP attacks, record the digital pulse after cold and heat stress and assess the severity of RP. Digital blood pressure reduction by 70% or more after local cooling can distinguish between primary and secondary RP with 97% sensitivity. A zero digital pressure at 30°C is associated with 100% specificity for SSc. Systolic pressure and skin temperature correlate inversely with the time to healing of digital ulcers. Measurement of the ratio of brachial to finger blood pressure is highest in SSc compared to other connective tissue diseases (16-21).

VI. Skin temperature
Values for basal skin temperature, temperature after cold stress and maximal recovery after cooling are abnormal in
patients with primary and secondary RP. The distal-dorsal temperature difference using a thermal camera can discriminate between primary and secondary RP. The test is reliable provided that it is done in a controlled environment (22, 23).

VII. Digital vascular response to endothelial-dependent and -independent dilators
The bulk of published studies suggest reduced endothelial-dependent vascular dilatation and somewhat preserved endothelial-independent dilatation. Vasodilator agents are given systemically or applied by iontophoresis. Nonetheless, results are difficult to reproduce and do not consistently distinguish between primary and secondary RP (24-26).

VIII. Cold pressor effect on organ perfusion
Hand cold challenge results in reduced organ perfusion as judged by laser Doppler flowmeter, 201thallium myocardial scintigraphy, pulmonary perfusion by 41M Krypton, and 133Xenon clearance of regional cerebral blood flow. Reversible reduction of organ blood flow is seen even in patients without clinical organ disease. In the heart, reversible myocardial perfusion defects with regional wall motion abnormalities and perfusion defects upon hand cold exposure have been reported, indicating the profound effect of digital ischemia on organ perfusion and the systemic nature of RP (27-30).

IX. Exercise performance
Unfortunately, few studies have evaluated overall circulatory performance in SSc. This approach provides a global assessment of circulatory function. However, further experience and refinement of the method are needed in order to adapt this technique for the clinical evaluation of SSc. Reduced O2 consumption, carbon dioxide production, the respiratory exchange ratio, O2 saturation, low O2 pulse and low QO2 consumption at anaerobic levels during exercise were reported in a comprehensive study, suggesting the presence of systemic circulatory impairment in SSc (31).

X. Transcutaneous oxygen pressure
Cutaneous PO2 measurement reflects local skin properties and blood flow. Decreased PO2 at rest and after arterial occlusion with a prolonged recovery time is reported in SSc. This test has good clinical potential but needs additional standardization (22, 32).

XI. Macrovascular disease in SSc
Large vessel occlusion in SSc is unusual, but may occur in the ulcer arteries, particularly in patients with ISSc in association with anticentromere antibodies. Several studies have reported an increased frequency of ulcer, carotid and lower extremity arterial disease, particularly in ISSc with no significant difference in the prevalence of standard cardiovascular risk factors (33-35).

XII. Nailfold capillary microscopy
This test is best performed using a wide-field stereoscope equipped with 12-100X magnifications and photographic capabilities. The most specific pattern is the presence of enlarged capillaries, particularly at the edge of the nailfold, and variable loss of capillaries. A less specific pattern is budding capillaries and hemorrhages. Extensive avascularity is associated with severe disease and with the number of involved organs, in contrast to budding and large capillaries that are correlated with stable disease. Early disease is associated with capillary loss while late disease is associated with enlarged vessels. Thus, the terms “active patterns” and “slow patterns” are suggested. The test has great diagnostic value in the early stages, but its prognostic potential is not well established. Some studies suggest the usefulness of the test in predicting organ involvement while others do not find the test to be useful. Decreased capillary density is associated with pulmonary hypertension in ISSc. Computer-based quantitative analysis of capillary drawings and quantitative TV microscopy of nailfold capillaries to assess venous plexus visibility, capillary density, avascular beds, hemorrhages, giant capillaries, vessel diameter, loop width and flow after cooling are some of the suggested variations to the test. These are involved techniques that require technical expertise and expensive equipment, however (36-39).

XIII. Circulating vascular markers
1. Soluble adhesion molecules: The overexpression of adhesion molecules in involved and uninvolved skin at the mRNA and protein levels in SSc are well established. Clinical correlations suggested that sP-selectin and sE-selectin levels correlate with early disease and with in situ expression of the molecules and possibly with lung fibrosis. sICAM-1 levels are elevated in early, rapidly progressive disease and in digital infarcts and correlate with the serum sIL-2 receptor level. sVCAM-1 levels correlate with left ventricular functional impairment, the presence of pulmonary fibrosis, joint involvement and increased ESR. Serial assessment of adhesion molecule levels have shown correlations between reduced levels of sVCAM and sE-selectin and improved skin scores and renal function, while increased levels are associated with worsening PFTs and may precede renal failure (40, 41).

2. Endothelin-1 level: ET-1 levels during RP attacks generally do not correlate with digital blood flow and the attacks themselves. Nonetheless, ET-1 levels do correlate with left ventricular hypertrophy, the ventricular mass index, and impaired left ventricular contractility and end systolic wall stress. In ISSc, levels correlated with pulmonary hypertension and with renal disease in dSSc. Other clinical studies have suggested a significant correlation with the wVF level, skin score, disease duration, and capillaroscopy cold test findings and an inverse correlation with the carbon monoxide diffusing capacity (42-46).

3. Nitric oxide: Plasma nitrate and 24-hour urinary excretion of cGMP are elevated in SSc and correlate with levels of sICAM-1, sVCAM-1 and sE-selectin (47).

4. Prostacyclin: Limited studies suggest increased prostacyclin plasma and urinary levels with no significant clinical correlations (48).

5. Coagulation and Fibrinolysis: Published data are controversial and still
Table I. Core set of vascular parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Core/Defined</th>
</tr>
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<tbody>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Present/absent</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>Present/absent</td>
</tr>
</tbody>
</table>

Table II. Characterization set of vascular parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Duration, frequency, severity, Raynaud’s condition score</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>Frequency, size, severity, no. of involved digits, VAS score</td>
</tr>
</tbody>
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Table III. Useful but not essential parameters.

- Color Doppler flow studies
- Post-occlusive hyperemic response
- Plasma vWF level
- Soluble adhesion molecules, particularly sVCAM-1
- Nailfold microscopy with attempt to describe “active” and “slow” patterns
- Transcutaneous O₂ pressure
- s-Thrombomodulin level
- Anti-endothelial cell antibodies

Discussion
Identification of core set variables
After extensive review of published studies and a critical assessment of proposed vascular parameters, the subcommittee has endorsed a minimal set of requirements for the documentation of vascular involvement in SSc. The core set variables include two parameters: Raynaud’s phenomenon and digital ulcers, i.e., the presence or absence of Raynaud’s phenomenon and digital ulcers (active or healed) should be reported (Table I). Both parameters can be further characterized (Table II).

Rationale for selecting the core set variables
The selection of this core set satisfied the objective that had been set. This core set of variables represents the minimal essential information for the clinician, it is simple to obtain, and it has been validated in multiple studies. The parameters do not require any special equipment or extensive expertise, and yet they represent a good and reproducible assessment of the vascular disease in SSc.

Rationale for the exclusion of other variables
A variety of invasive and non-invasive parameters that reflect vascular performance in SSc have been suggested in the literature. Most have not been well characterized, documented or tested in homogenous population. Others require sophisticated instruments and extensive expertise. The subcommittee recognizes that most would not satisfy the constraints of minimal core set variables, although it has identified certain vascular parameters that may potentially become significant in the assessment of vascular disease in scleroderma in the future; these parameters are listed in Table III.

References
4. CLARK S, CAMPBELL F, MOORE T et al.;


