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Invited Review

New perspectives in the imaging of Raynaud's phenomenon

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Abstract

The last 10-20 years have seen huge strides in imaging science. The aim of this review article is to share with the reader the key recent advances in non-invasive imaging of the digital (finger) vasculature in patients with Raynaud's phenomenon (RP), including in systemic sclerosis (SSc)-related digital vasculopathy. For the rheumatologist, seeing a patient with RP is an opportunity for early diagnosis of an underlying SSc-spectrum disorder or (conversely) for reassuring the patient with primary (idiopathic) RP. Non-invasive imaging techniques can help to provide diagnostic certainty. In addition, they can provide new insights into pathophysiology and have the potential to facilitate the development of much needed effective treatments by providing primary and secondary endpoints for randomized controlled trials: validation studies are ongoing. This review article focuses on nailfold capillaroscopy, thermography, and laser Doppler methods but also discusses (briefly) other technologies, including optical coherence tomography, multispectral imaging, and photoacoustic imaging. Key recent advances are the increasing use/availability of nailfold capillaroscopy (and better understanding of the role of low-cost hand-held devices), increased accessibility of thermography (including mobile phone thermography), and increased application of laser Doppler methods to the study of RP/digital vasculopathy (in particular of laser Doppler imaging and laser speckle contrast imaging, both of which measure blood flow over an area rather than at a single site). In an era of precision medicine, non-invasive imaging techniques can help stratify risk of (a) SSc in the patient with RP and (b) digital vascular disease progression in the patient with an SSc-spectrum disorder.

Keywords: Raynaud's phenomenon, nailfold capillaroscopy, thermography, laser, Doppler, optical coherence tomography

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Introduction

Imaging science is making rapid strides, and the last 10 years have seen significant progress in terms of developing and validating different non-invasive imaging methodologies used to assess Raynaud's phenomenon (RP). This has implications for both clinical practice and research because of the following reasons:

1. Non-invasive imaging techniques allow separation between primary (idiopathic) and secondary RP. In addition to aiding diagnosis, these techniques afford unique insights into pathophysiology, allowing us to recognize important differences between primary and secondary RP in terms of vascular structure and function.
2. Non-invasive techniques can provide objective outcome measures to study disease progression and (importantly) treatment response. As rheumatologists, we badly need reliable outcome measures, which are sensitive to change, to act as primary and secondary endpoints in clinical trials. Current treatments are not ideal, and one of the factors mitigating against randomized controlled trials has been the lack of outcome measures: the Raynaud's condition score (RCS) is the only validated outcome measure (1), but is subjective. However, this situation is now changing (2).

This review will give a broad overview of the different non-invasive imaging methods, which can help in assessing the digital vasculature in patients with RP, with a focus on recent advances and new perspectives. Both clinical and research applications will be discussed. We shall focus on nailfold capillaroscopy, thermography, and laser Doppler methods but shall also discuss (albeit briefly) some exciting emerging technologies, specifically optical coherence tomography (OCT), spectroscopy and multispectral imaging, photoacoustic imaging, and power Doppler ultrasound. More detailed descriptions of the individual techniques can be found elsewhere, and for a comprehensive technical review, the reader is referred to the review by Allen and Howell (3). We shall not discuss arterial Doppler ultrasound, although this is, of course, a key first

investigative step if there is any question that large vessel disease is contributory to digital ischemia in the patient with RP (e.g., unilateral symptoms and/or absent peripheral pulses, especially in the context of critical ischemia, including in the patient with known systemic sclerosis [SSc]) (4).

SSc-related RP is the form of secondary RP, which has been most researched, and therefore will be most discussed in this review. A key difference between primary and SSc-related RP is that in SSc, digital vascular disease is structural as well as functional, that is, the vasospasm, which is the hallmark of RP, is superimposed on a structurally abnormal digital vasculature (at both digital artery and microcirculatory level). In contrast, primary RP is a purely functional problem (vasospasm followed by reactive hyperemia) and is entirely reversible—it does not progress to irreversible tissue injury (5, 6). One of the major implications of this is that in terms of treatment, SSc-related RP is far more challenging to the rheumatologist than primary RP, and the quest for new treatments is more pertinent. However, in terms of population morbidity, primary RP carries a large burden because approximately 5% of the population are affected (7), in many of whom RP impacts on the quality of life (8), and patients with primary as well as secondary RP report that current treatments are often ineffective (8).

Nailfold capillaroscopy

Rationale and background

At the nailfold, capillaries lie parallel instead of perpendicular to the skin surface. Easy, non-invasive visualization is possible through a number of capillaroscopic methods described below. Enormous advances have occurred in the last 20 years (9, 10), with increasing uptake of capillaroscopy among rheumatologists over this time. It is now well-recognized that in the patient with RP, abnormal nailfold capillaries are a definite red flag for the development of SSc (11, 12) and an independent predictor of SSc (13). These observations have culminated in abnormal nailfold capillaries being included in the classification criteria for SSc (14). Thus, any clinician involved in diagnosing SSc must have access to capillaroscopy: otherwise an early diagnosis might be missed. Training courses (including the biennial European League Against Rheumatism course, since 2004) are well subscribed, and a recent survey of 42 US rheumatologists with an interest in SSc indicated that 76% would like more formal training in capillaroscopy (15).

Main Points

- Non-invasive imaging techniques help to differentiate between primary and systemic sclerosis spectrum disorder-related Raynaud's phenomenon and provide insight into pathophysiology.
- The last 20 years have seen major advances in nailfold capillaroscopy, thermography, and laser Doppler methods: a key challenge is to standardize imaging protocols.
- Several non-invasive imaging techniques hold promise as outcome measures in clinical trials.
- New emerging technologies relevant to the assessment and study of Raynaud's phenomenon include optical coherence tomography, multispectral imaging, and photoacoustic imaging.

Different methodologies

The original method used by Maricq (16) for viewing and imaging the nailfold capillaries in her seminal papers in the 1970s was widefield microscopy, which visualized the whole nailbed. This technique allowed the recognition of the now famous scleroderma pattern, characterized by capillary enlargement, areas of avascularity (capillary drop-out), distortion of the normal nailfold architecture, and hemorrhages and later subdivided into early, active, and late patterns by Cutolo et al. (17). The widefield microscope (stereomicroscope) is now seldom used, and the gold standard is now taken to be nailfold videocapillaroscopy. However, videocapillaroscopy is relatively expensive and unlikely to be available to all rheumatologists. Here, we briefly describe the different techniques (Figure 1), with key points summarized in Table 1 to help readers choose which might be most useful to them. Note that for all techniques, a drop of oil (olive oil or other colorless vegetable oils are good choices) should be applied to the nailfold: this increases the capillary visibility by reducing the effect of light scattering at the skin surface.

Nailfold videocapillaroscopy. A number of systems are commercially available, some using a hand-held (direct contact) probe, others a fixed microscope. An advantage of a hand-held probe is that patients with flexion contractures of their fingers (common in SSc) can be examined (this is often very challenging with a fixed microscope). Videocapillaroscopy has high resolution (typical pixel sizes are around 1 µm) and therefore allows detailed information to be extracted from individual capillaries. It allows measurement of capillary density (number of distal vessels per millimeter across the nailbed) and individual capillary dimensions—very useful in research practice and also to the clinician. For example, a normal capillary density is generally accepted to be 6-10 capillaries/mm (18, 19), and normal apical widths can typically range between 10 and 25 µm. Any vessel having an apical width of more than 50 µm is generally considered pathognomonic of SSc. However, with most commercially available systems, only a relatively narrow field of view (1-2 mm) is captured; thus, depending on the clinical or research question, a series of frames must be captured to ensure that the whole nailfold is examined. This is important because in any one individual, nailfold capillaries vary both within and between nailbeds.

Stereomicroscope. This is a fixed microscope that has the advantage of both high resolution and a wide field of view. Disadvantages are lack of portability and expense.

Dermatoscope. This portable device captures a widefield view (lower magnification) and compares favorably to nailfold videocapillaroscopy in terms of ability to classify (i.e., to be able to visualize the capillaries sufficiently clearly to grade them) and to grade images (20). As might be expected, the dermatoscope is less sensitive, but more specific, in detecting abnormality compared with videocapillaroscopy (20).

USB microscope. These cheap, consumer-grade devices have been studied less but have the advantage of being portable and are very inexpensive (at the time of writing, it can be purchased on the internet for around $35). The images produced are usually of comparable quality with the dermatoscope, although integrated lighting is not necessarily optimized for capillaroscopy and thus can cause more glare than other techniques. It seems highly likely that for the general rheumatologist, the USB microscope will become a preferred option.

Opthalmoscope. This gives a very narrow field of view, but can be used to observe obvious abnormalities, for example, giant capillaries (homogenously enlarged with a diameter in excess of 50 µm) and hemorrhages.

Clinical indications and key messages for clinicians

The main clinical indication for capillaroscopy is assessment of the patient with RP. Visualization of normal capillaries allows the patient to be reassured (unless there are clinical or serological features of concern). Conversely, abnormal capillaries in a scleroderma pattern means that the patient must be kept under

Table 1. Properties of different capillaroscopic methods to be taken into account before purchasing a system for clinical or research use.

Property	NVC	Stereomicroscope	Dermatoscope	USB	Opthalmoscope
Magnification	High	Variable	Low	Variable	High
Resolution	High	High	Medium	Medium	Low
Whole field of view?	No[a]	Yes	Yes	Yes	No
Measurement of density and capillary dimensions?	Yes	Maybe	No	Maybe	No
Easily portable?	Depends on system	No	Yes	Yes	Yes
Image capture?	Yes	Yes	With attached camera	Yes	No
Cost	$5-12,000	$7,000	$2,000	$35	$700

[a]But possible via image mosaic.
NVC: nailfold videocapillaroscopy.

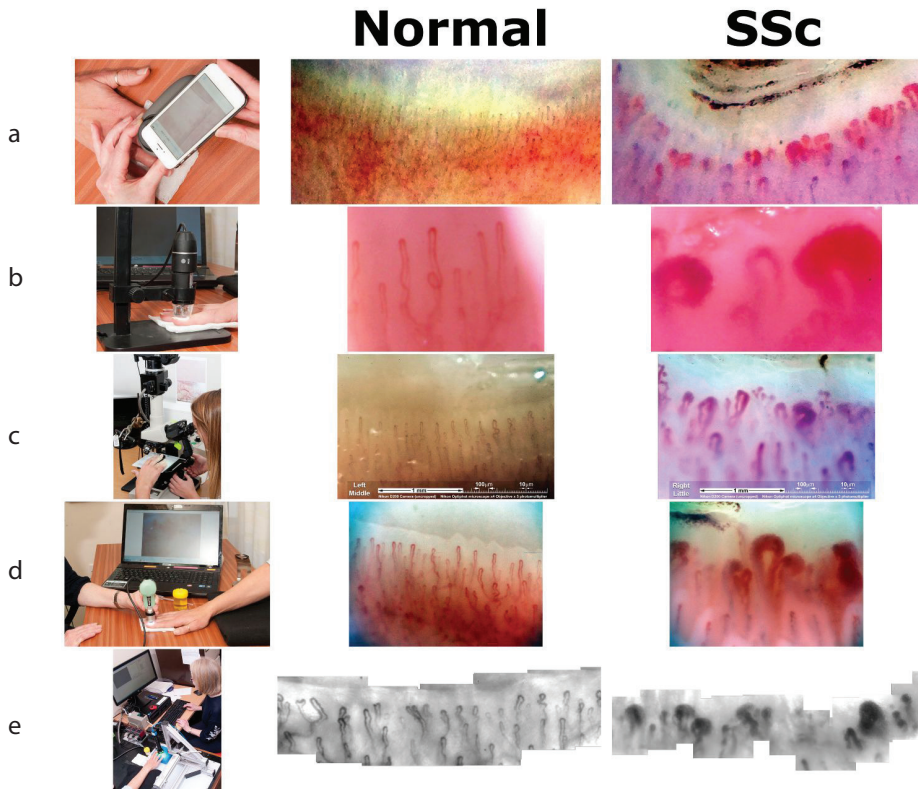

Figure 1. a-e. Capillaroscopy techniques (left column) and example images (center column: normal appearance, right column: abnormal/systemic sclerosis (SSc) appearance). Dermoscopy—a low-magnification technique using a hand-held dermatoscope to either directly view the nailfold or (in conjunction with a camera or adapted smartphone) produce images as shown (a); USB microscope—a very low-cost, hand-held option providing usable, low-resolution images (b); Widefield microscope—a fixed microscope in conjunction with a digital camera gives high-quality images of the entire nailbed (c); A hand-held nailfold capillaroscopy-specific videomicroscopy system producing high-magnification images of small (approximately 1 mm) sections of the nailbed (d); The Manchester system—a bespoke high-magnification videocapillaroscopy solution producing mosaic images of the entire nailbed at high resolution, together with high speed video data capture for measuring capillaroscopy blood flow (e).

review and investigated for other features of an underlying SSc-spectrum disorder, for example, internal organ involvement. Sometimes capillaroscopy findings are equivocal (not normal but not diagnostically abnormal), in which case the patient should be reviewed and the capillaroscopy repeated in 6-12 months. As discussed under the point "reliability," it is important to recognize that nailfold capillaries cannot always be visualized, and this is especially true in individuals with darker skin.

Role in research

It is outside the scope of this review to give a comprehensive overview of capillaroscopy research, but we have summarized the main areas of recent research relevant to RP (and especially to SSc-related digital vasculopathy):

1. Reliability. Any method to be applied in clinical practice or research must be reliable. Reliability has been addressed in several studies (recent ones including (21-24)). There are several aspects to consider: reliability of qualitative image grading (e.g., early, active, and late); reliability of semi-quantitative and quantitative measures, including capillary density and apical width; presence of giant capillaries; and the reliability of image acquisition (23).

   A complicating factor is that the nailfold capillaries cannot always be clearly seen and therefore cannot be evaluated. Assessment of evaluability varies between observers and needs to be taken into account when assessing reliability: in a recent study involving 10 expert raters, 73% of images from patients with SSc were evaluable in terms of capillary density and presence/absence of giant capillaries but only 46.2% in terms of image grade (22). At the individual capillary level, a proportion of images are still considered to be not evaluable (21).

2. Capillaroscopy as a predictor of disease severity. Several studies have shown that in the patient with SSc, the degree of capillaroscopic change is a risk factor for future digital ulceration (25-27). A recent review highlighted the inherent complexities of using capillaroscopy as a prognostic tool (28). Nonetheless, capillaroscopy holds promise in a stratified medicine approach to treatment.
3. Capillaroscopy as an outcome measure. Changes in nailfold capillaroscopy have been reported in response to a number of different drug treatments, and capillaroscopy has also been suggested as a monitoring tool for the SSc disease process (29). A word

of caution—it is imperative that investigators ensure that the same set of capillaries is examined each time, given the heterogeneity in appearances between and within nailfolds. If different capillaries are examined, a very different result can be obtained (30), irrespective of any drug treatment. The small field of view of commercially available videocapillaroscopy systems can make it very difficult to ensure that exactly the same capillaries are examined each time. Although there have been some promising reports, in the authors' opinion, the full potential of nailfold capillaroscopy as an outcome measure has yet to be realized: automated analysis should facilitate this.

4. Automating analysis. Qualitative analysis is subjective. Quantitative analysis is time-consuming when done manually. Methods of automating analysis are therefore being explored. Cutolo et al. (31) have described a method of automatically counting capillaries within an observer selected 1 mm section of nailfold. A fully automated method of analyzing capillaries in terms of density, apical width, tortuosity, and derangement across a whole nailfold has been developed and performs as well as a human expert (32). More recently, this method has also incorporated measurement of blood flow velocity (33).

Recent advances and future directions

Key recent advances include increased understanding of how the different techniques compare (especially dermoscopy to videocapillaroscopy), automation of quantitative analysis (although this is not yet widely available), and increased understanding of the potential (and the caveats) of capillaroscopy as an outcome measure in longitudinal studies. The challenges for the future are standardizing image acquisition and image interpretation and ensuring increased uptake by all rheumatologists involved in assessing patients with RP and possible connective tissue disease, to ensure early diagnosis of an underlying SSc-spectrum disorder.

Thermography

Rationale and background

Infrared thermography measures surface temperature and is therefore an indirect measure of blood flow when imaging skin. Therefore, it assesses (albeit indirectly) vascular function and complements the structural assessment obtained by nailfold capillaroscopy. For many years, the use of thermography in the assessment of RP has been confined to specialist centers because of the need for expensive equipment and a temperature- and humidity-controlled laboratory (9). However, as discussed below, this could now change.

Different methodologies

With advances in technology, thermal cameras are much more portable and compact than previous models, and a recent improvement has been the development of a low-cost mobile thermal camera, which attaches to a mobile phone or tablet (Figure 2). These mobile devices have wider limits of accepted accuracy than standard thermal cameras: mobile devices range up to ±5% from the real temperature (data unpublished) compared with ±2% for more specialist devices (34). Nonetheless, it will be interesting to see whether low-cost thermography gains momentum as a clinical tool. Irrespective of the device used, environmental conditions must be controlled and standardized as much as possible to minimize physiological variability.

In the setting of RP, thermographic protocols often incorporate some form of temperature challenge—usually cold (35-38) but sometimes heating (36). Differences in responses help to differentiate patients with primary and SSc-related RP and healthy controls. Such challenges have also been used to assess treatment responsiveness. A major problem has been the lack of standardization between protocols (in terms of equipment used, the type of temperature challenge, and the parameters derived from the baseline and rewarming images (39)), but this is now being addressed as discussed below (2). Some investigators have suggested that in differentiating between primary and secondary RP or between patients with RP and controls, a baseline image performs as well as a cold challenge and is much simpler (40-42) although possibly less reproducible (2).

Clinical indications and key messages for clinicians

As already stated, thermography can help to separate primary from secondary RP. Patients with SSc-related RP have structural changes in the digital arteries and microcirculation with a reduction in baseline blood flow, which typically after a cold challenge does not revert to normal with rewarming/heating. This is in contrast to the situation in primary RP when the fingers typically rewarm (Figure 2). We reported that in a study of 16 patients with SSc, 14 patients with primary RP, and 16 healthy controls (43), 74% of patients were correctly classified (as having SSc or not) using thermography, compared with 89% with capillaroscopy. A combination of capillaroscopy, thermography, and laser Doppler imaging (LDI) correctly classified 94%, suggesting that discrimination is improved by combining structural and functional techniques (43).

Role in research

Thermography's main role in research has been as an outcome measure in clinical trials, and several recent studies have included thermography in assessing treatment response (reviewed in (37) and (39)). A report from Outcome Measures in Rheumatology (6) suggested that it was premature to include non-invasive imaging methods as outcome measures as these were not yet validated (44). A recent UK study involving 159 patients with SSc-related RP from six centers (2) showed that responses to a cold challenge, measured by either thermography or laser speckle contrast imaging (LSCI), provided reliable outcome measures (especially area under the rewarming/reperfusion curve and the maximum skin temperature/blood flow following rewarming). Measurements made by mobile phone thermography compared favorably with those by standard thermography (2), paving the way for ambulatory monitoring in non-controlled environments to increase understanding of RP episodes.

Similar to the situation with capillaroscopy, severity of change (on thermography) may predict digital ulcer risk in patients with SSc (45).

Recent advances and future directions

The key recent advances are as follows:

1. Increased accessibility of equipment. It is possible that mobile phone thermography will overcome the difficulties in implementation referred to by Maverakis et al. (46) when discussing the use of thermographic imaging in the diagnosis of RP.
2. Validation of a cold challenge protocol for use in treatment response studies (2).

Increased use of thermography in clinical studies of RP makes sense—after all, what the patients complain of is cold hands—thermography gives an objective assessment of this.

Laser Doppler methods

Rationale and background

The Doppler effect is inherent to all laser Doppler techniques (3). Laser light entering tissue interacts with tissue components and can be backscattered out toward a detector. The wavelength or color of the light exiting the tissue is changed if it has been scattered from moving cells (mainly erythrocytes), but it is not changed when interacting with stationary structures such as collagen. The color change is directly proportional to the speed and con-

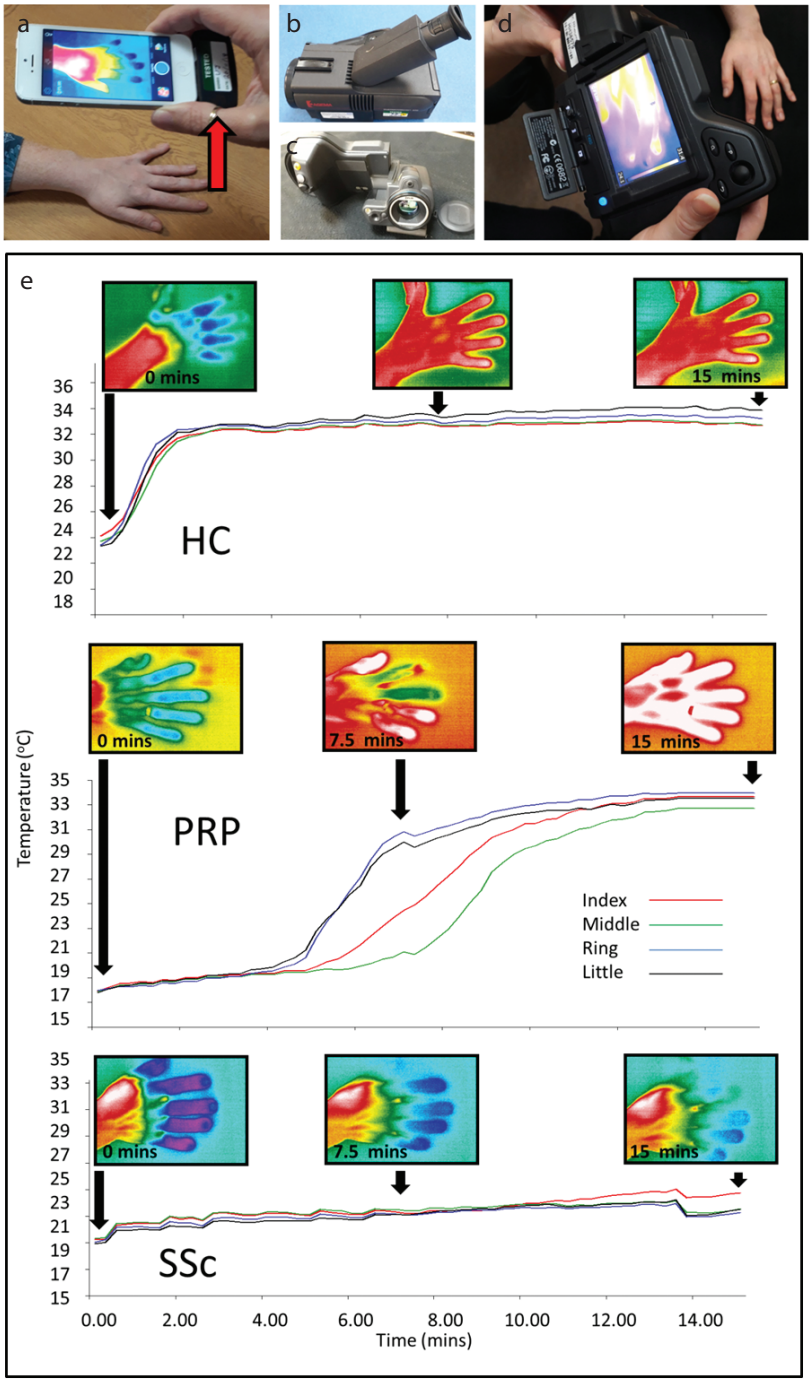

Figure 2. a-e. Thermography. Mobile phone thermography with camera (indicated by arrow) attached to phone and phone shows live image of skin temperature (a); Older, larger model thermal camera with eye piece for viewing live images (b); Newer, smaller model thermal camera ((c) front view and (d) back view) with built-in screen for reviewing images live; Three rewarming curves, following finger cooling (cold challenge at 15 °C for 1 min) (e). Top curve shows a "normal" rewarming for a healthy subject with time (skin temperature on the y-axis). Each finger is represented by a colored line (see key on figure) showing a 15-minute rewarming period at a room temperature of 23 °C. Images of hands are representative at time-points shown by arrows. The middle curve shows the same for a patient with primary RP; note the different rates of rewarming of the fingers. The bottom curve is for a patient with systemic sclerosis (SSc) and shows a noticeably lower response than for a patient with primary Raynaud's phenomenon (RP).

centration of red blood cells, thus providing a measurement of blood flow. Measurements are described in arbitrary flux units because they are relative rather than absolute. Most laser Doppler systems use red and/or infrared wavelengths and allow imaging in human skin to a depth of approximately 1 mm; using a shorter wavelength (e.g., green light) reduces the imaging depth and confines examination to the more superficial microvessels (47, 48).

Most laser Doppler studies in patients with RP used a single-point technique 20 years ago (flowmetry (9)). LDI, examining an area rather than a single point in RP, was just emerging. Since then, LDI and more recently LSCI, also called laser speckle contrast analysis have been used to examine finger blood flow in patients with RP, compare primary and secondary RP, examine treatment response, and study SSc-related digital ulceration.

Different methodologies

Three methods will be described briefly: laser Doppler flowmetry (LDF), LDI, and LSCI (Figure 3) (3, 37, 47). These are all research tools: at present, they are not used in routine clinical practice.

LDF (also termed anemometry or velocimetry). LDF provides a continuous recording of perfusion—useful in monitoring response to a specific, transient stimulus such as a temperature challenge, or reperfusion hyperemia. The disadvantages are as follows: (1) the small volume of skin sampled (typically a few mm^3) may be unrepresentative of skin blood flow, given the heterogeneity of the cutaneous microcirculation (the readings are extremely site/position-dependent); (2) LDF usually requires direct contact with the skin (contact can affect blood flow) but if done 'non-contact,' where the laser is projected onto the skin, it is much more prone to movement artifacts. For these reasons, LDI and LSCI (both imaging blood flow over an area) are now more widely used. However, LDF continues to be used (49, 50) for dynamic blood flow monitoring and can often be carried out using an LDI system with the laser held at a single location. Novel developments in LDF systems include coupling to other devices to allow simultaneous monitoring of, for example, temperature and transcutaneous oxygen (51).

LDI. LDI allows non-contact measurement of tissue perfusion over an area. Images are formed by raster scanning or line scanning a laser across the skin (Figure 3), the latter allowing faster image capture. Faster scans are more desirable for monitoring the effects of dynamic stimuli in tissue. Imaging can minimize movement artifacts associated with LDF by allowing adjacent pixels to be averaged; it also allows larger regions of interest to be selected for measurement of perfusion.

LSCI. LSCI allows full-field imaging (no scanning required) (52). This technique utilizes a property of laser light called coherence, which produces a speckle pattern (black and white noise) when a laser hits a rough surface, that

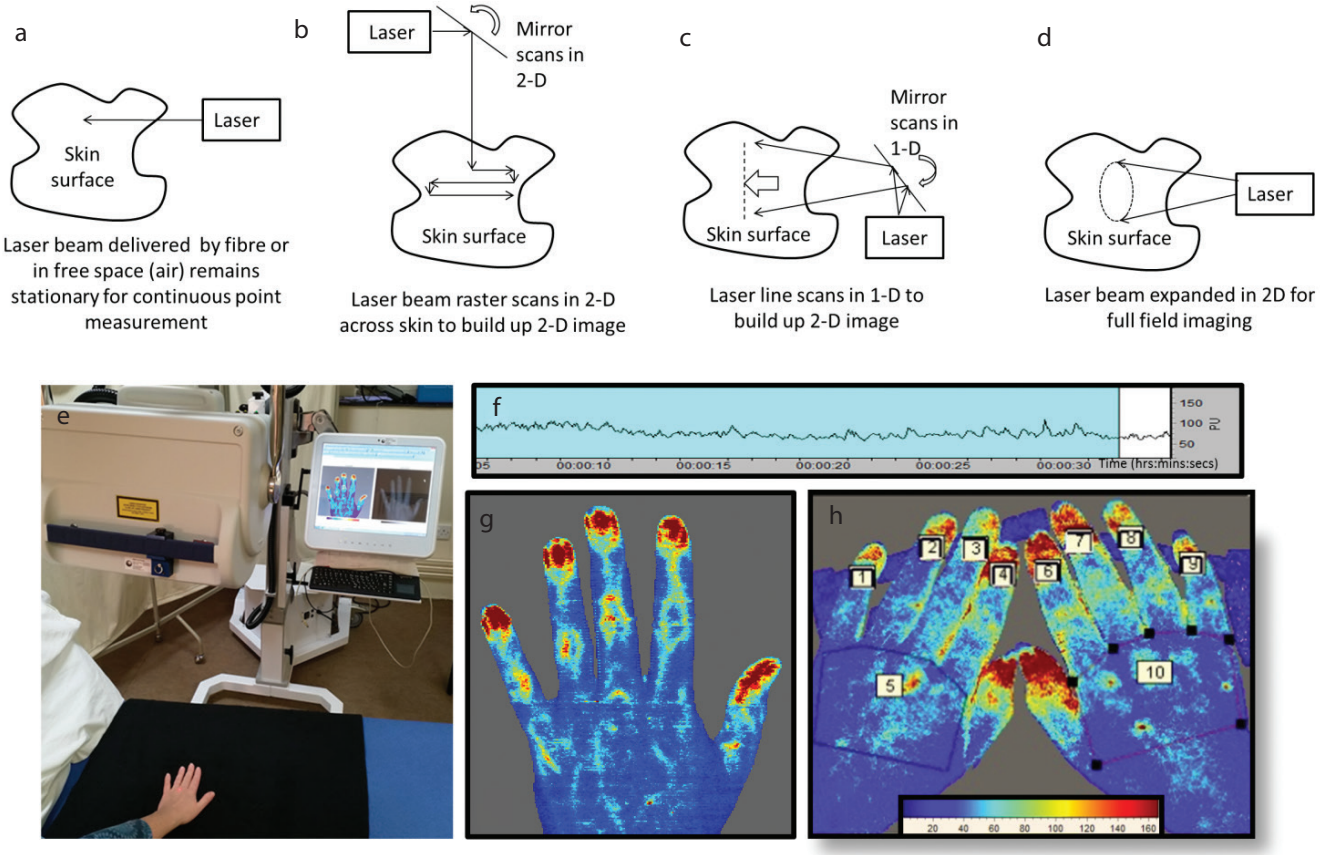

Figure 3. a-h. Laser Doppler methods. Showing schematics for laser Doppler flowmetry (LDF), raster scanning laser Doppler imaging (LDI), line scanning LDI, and laser speckle contrast imaging (LSCI), respectively (a-d); Example of LDI in use with completed scan on screen (e); LDF graph of baseline perfusion (arbitrary perfusion units [PU]) of the finger with time (f), taken on the LDI shown in (e); LDI scan of the hand at baseline, false colors, with blue representing lower and red relatively higher flow (g), also taken on the LDI shown in (e); LSCI scan of the hands at baseline, arbitrary PU scale shown at the base of the image (h). Fingers and dorsum of each hand show as regions of interest 1-10.

is, non-mirror-like surface. If the surface is stationary, then the pattern is unchanging. If there is movement, as with blood flow in skin, then the pattern changes in a manner related to the flow. The laser beam is expanded over an area and the returning light is captured by a charge-coupled device camera. The advantages of LSCI are rapid (video-rate), full-field imaging allowing monitoring of dynamic events over a large area with good spatial and temporal resolution, as well as eye-safe equipment. However, it should be noted that the light does not penetrate to the depths possible with LDI, thus limiting imaging to the more superficial microcirculatory layers.

Role of laser Doppler methods in research

It is beyond the scope of this review to give a detailed critique of the different studies applying laser Doppler methods in patients with RP and SSc-related digital ischemia (a much more comprehensive overview can be found in (37)). However, some general points will be made.

1. Laser Doppler methods can help to differentiate between patients with primary and SSc-related RP and healthy controls (43, 53, 54). Although pathophysiologically it is important to assess blood flow abnormalities in patients with different forms of RP compared with healthy controls, the more pertinent question is how SSc-related RP differs from primary RP. As with thermography, results of both baseline and dynamic testing will be influenced by whether or not there is an underlying structural vascular defect such as that which occurs in patients with SSc.
2. Multiple studies, including some very recent ones (49, 50, 55-57), have used laser Doppler methods as outcome measures to assess treatment response (reviewed in 37), not only to different classes of drugs but also to procedural treatments, including botulinum toxin injections (58) and fat grafting (59). Varying protocols make it difficult to compare studies (as with thermography).
3. For laser Doppler methods to be used as outcome measures, they must be reliable. A number of studies within the last 10 years (complementing earlier studies) have assessed reproducibility/reliability of finger/hand or forearm blood flow using different protocols—some assessing reliability of baseline measurement (60, 61) and others including reliability of different dynamic challenges (62, 63). The six-center study of 159 patients with SSc-related RP aforementioned under "thermography" incorporating a cold challenge (2) reported good reliability for LSCI as well as of thermography.
4. Severity of vascular change, as measured by LSCI may be a risk factor for digital ulceration (64).
5. Some cross-sectional studies have looked for associations between laser Doppler and other non-invasive measures: results have differed between studies but, as might be expected, laser Doppler results have been reported to correlate with thermography (2, 63, 65) and with capillaroscopy (the more severe the capillaroscopic change, the lower the finger blood flow) (64, 66). However, only poor correlation has been reported between laser Doppler and the subjective RCS (2, 67), raising the broader issue (not discussed here) of the complexity of RP as a symptom complex (68).

Recent advances and future directions

Key recent advances from the perspective of the clinical researcher are the introduction of

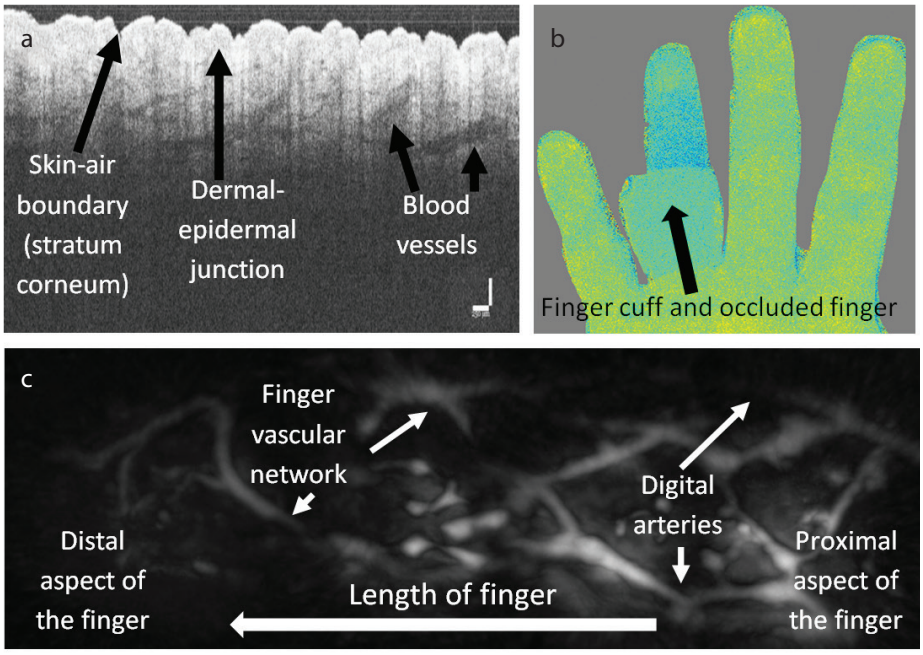

Figure 4. a-c. Emerging technologies. Optical coherence tomography (OCT) into depth of skin: stratum corneum, dermal epidermal junction, and blood vessels indicated by arrows (a). Bars represent 250 µm; Multispectral image of skin oxygenation with finger under occlusion (b). Occluded finger marked with arrow, blue indicates lower oxygenation compared with green; Photoacoustic image of reconstructed finger vascular network showing digital arteries and larger vessels as a network of white lines, highlighted by smaller white arrows (c). Larger arrow pointing from proximal toward distal phalanx.

LSCI (allowing rapid measurement of finger/hand perfusion) and the validation of a standard protocol for dynamic testing (although the performance of this protocol in assessing treatment response has yet to be tested).

Emerging technologies

There are a number of exciting new technologies that hold promise in the study of RP from two perspectives: first, increasing our understanding of pathophysiology and second, potentially providing outcome measures, which are sensitive to small but clinically relevant changes. These new technologies include OCT, multispectral imaging, photoacoustic imaging, and power Doppler ultrasound. Although it is not possible in this broad review to go into any detail, key points of each are given below.

OCT (Figure 4a) is a light interferometry technique analogous to ultrasound, providing images into the skin with a resolution of approximately 10 µm to a depth of 1-3 mm (69, 70). Dynamic-OCT images incorporate speckle measurements, which can increase the contrast of vascular network morphology allowing quantification of visible vessel volume and function (as a pseudo measure of flow) (71). Future advances may include perfusion and spectroscopic analysis to allow measurement of real-time function, for example, blood flow and differentiation of tissue types or measurement of oxygenation in vessels.

Single-point spectroscopy and multispectral imaging (Figure 4b) are techniques based on the analysis of backscattered white light from skin and can give information on erythema, melanin, and oxygenation in tissue (72, 73). Ultraviolet light can be used to induce skin auto-fluorescence, providing a measure of oxidative stress (74, 75).

Photoacoustic imaging (Figure 4c) combines the strengths of light and ultrasound imaging and overcomes some of their individual constraints for imaging vessel structure in three dimensions. The photoacoustic technique uses a pulsed, multi-wavelength laser, allowing preferential absorption by blood vessels and measurement of oxygenation (76-79). Hemoglobin, an endogenous contrast agent, absorbs the light, causing vessel heating and expansion; though between pulses vessels cool and contract. Thus, a "vibration" at ultrasonic frequencies is established and can be detected by an ultrasound transducer.

Power Doppler ultrasound provides images of Doppler amplitude rather than direction and speed as per conventional Doppler ultrasound. Improved sensitivity compared with standard Doppler ultrasound facilitates the detection of lower perfusion and smaller vessels. Power Doppler has been studied as a technique to differentiate between primary and secondary RP (80).

Conclusion

There have been significant recent advances in the application of non-invasive imaging techniques to the assessment and study of RP and SSc-related digital vasculopathy. For the clinician, the most relevant one at present is increased availability/usage of nailfold capillaroscopy. In addition, it is likely that thermography may become more widely used given the increased accessibility of the equipment (including mobile phone thermography). For the researcher, several techniques hold promise as outcome measures in clinical trials, and the key challenge for the next 5 years is to standardize protocols and to raise awareness and knowledge of the different techniques among rheumatologists with an interest in RP and SSc-spectrum disorders (81).

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