The Different Photoplethysmographic Patterns Can Help to Distinguish Patients With Primary and Sclerodermic Raynaud Phenomenon

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Abstract: *Introduction:* The aim of this study is to investigate pulsatility of digital arteries of hands by means of photoplethysmography (PPG) in patients with primary Raynaud phenomenon (PRP) and systemic sclerosis (SSc) and to compare the results with those obtained in healthy controls. *Methods:* One hundred five patients with SSc, 96 patients with PRP and 85 healthy controls were recruited in this study. Nailfold videocapillaroscopy and PPG were performed in healthy controls and patients. In patients with SSc, the capillaroscopic pattern was classified as early, active and late group pattern. A baseline PPG was recorded simultaneously in all 10 fingers of the hands. The photoplethysmographic curves were evaluated for morphology and amplitude of sphygmic wave. *Results:* In healthy controls group, PPG shows the presence of photoplethysmographic homogeneous pattern and high mean value of sphygmic wave amplitude. In PRP group, PPG demonstrates homogeneous photoplethysmographic pattern and low mean value of sphygmic wave amplitude. Finally, in the SSc group, photoplethysmographic pattern is dyshomogeneous, and the mean value of sphygmic wave amplitude is intermediate between the other 2 groups. The PPG findings are different in the 3 capillaroscopic groups of patients with SSc and 2 subsets of disease. *Conclusion:* PPG represents a technique noninvasive to evaluate simultaneously in all 10 fingers of hands digital arteries pulsatility. PPG improves the evaluation of vascular damage in patients with primary and sclerodermic RP.

Key Indexing Terms: Photoplethysmography; Raynaud phenomenon; Systemic sclerosis. **[Am J Med Sci 2010;340(6):457–461.]**

The term Raynaud phenomenon (RP) is used to describe the episodic events that represent vasoconstriction of the digital arteries, precapillary arterioles and cutaneous arteriovenous shunts. It typically starts in 1 or several digits after exposure to the cold or a stressful situation and then spreads symmetrically to all fingers of both hands. Primary Raynaud phenomenon (PRP) is characterized by symmetric attacks, absence of tissue necrosis, ulceration or gangrene, absence of a secondary cause, normal nailfold capillaries, a negative test for antinuclear antibodies, normal erythrocyte sedimentation rate and normal value of the C-reactive protein.[1,2] Systemic sclerosis (SSc) is a disorder characterized by alterations of the microvasculature, dysfunction of the immune system and deposition of collagen in connective tissue. Vascular impairment, a main feature of the pathogenesis of SSc, involves both the macro- and the microvasculature. Vascular symptoms are the major prognostic factors for SSc, with a following general outcome depending on the extent and severity of vascular lesions.[3] Irrespective of the classification of the disease, SSc is typically associated with RP.[4] RP secondary to SSc is characterized by microvascular damage and high plasma adrenomedullin and endothelin-l levels.[5–7]

Capillaroscopy is crucial to differentiate between PRP and secondary RP.[8,9] Actually nailfold videocapillaroscopy (NVC) represents the best method to analyze microvascular damage in rheumatic diseases. In healthy subjects, the microvascular pattern is characterized by a regular array of microvessels with large intra- and interindividual variability. The presence of megacapillaries and a decreased capillary density are the hallmarks of the SSc capillary pattern, which can be detected by nailfold capillaromicroscopy. Recently, 3 defined major NVC patterns have been considered useful for assessing the appearance and the progression of sclerodermic microangiopathy ("early," "active" and "late" patterns).[10,11] Today, noninvasive and invasive examination techniques have become a common method of assessing peripheral vascular perfusion: color-coded duplex Doppler ultrasonography, angiography, computed tomography, magnetic resonance angiography and laser Doppler perfusion image.[12–15]

Actually, photoplethysmography (PPG) occupy a indefinite position among these methods in the RP assessment. The first photoelectric plethysmography was described in the 1930s. Today, PPG systems operate in near infrared light and allow the transcutaneous registration of venous and/or arterial blood volume changes in the skin vessels. In this wavelength range, hemoglobin in the blood absorbs much more strongly than the remaining tissue. Wavelengths around 900 nm are most suitable because they combine good penetration with good contrast between the dark vessels and the light tissue. The simplest PPG sensor consists of an IR-LED and a photodetector. In quantitative PPG, the optical illumination is automatically adjusted for each different type of skin until a predetermined level of reflected light is reached. With this technology, PPG measurements are independent of skin color, thickness and individual blood volume, so that interindividual registrations and registrations with different devices can be compared. Arterial PPG detects the pulse-related changes in skin blood volume and has a limited penetration depth, reflecting pulsatile blood volume changes of the skin including the plexus.[16] The main applications of PPG include the muscle pump test (assessment of calf pump failure in chronic venous insufficiency), vein occlusion test (thrombotic obstruction), venous resting pressure test, arterial perfusion test, peripheral arteriosclerosis quantification, vascular responses to drugs, macro- and microcirculatory assessment of cold sensitivity after traumatic finger amputation and microsurgical replantation.[17–19]

PPG was also used to quantify the vascular damage in hand-arm vibration syndrome. Therefore, its application in RP is limited to evaluate response of digital arteries to cold test and drugs.[20,21] This study was designed to assess whether PPG can help to distinguish likely patients with idiopathic and sclerodermic RP.

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TABLE 1. Epidemiological and clinical features of the patients with SSc (n = 105)

Sex (female/male)	94/11
Age (mean ± SD) (yr)	55.6 ± 12.6
SSc duration since diagnosis (yr), mean ± SD	7.2 ± 17.5
Raynaud phenomenon duration (yr), mean ± SD	13 ± 110.5
Subset[a] (n) dcSSc/lcSSc	41/64
ANA pattern, n (%)	
Speckled	20 (19)
Speckled and nucleolar	12 (11)
Nucleolar	20 (19)
Centromere	53 (50)
SSc-specific autoantibody, n (%)	
Antitopoisomerase I	33 (31)
Anticentromere antibody	53 (51)
None	19 (18)
DAI[b]	2.1 ± 11.8
DSI[c]	4.5 ± 12.6

[a] Subset according to LeRoy et al.[23]
[b] Disease Activity Index (DAI) according to Valentini et al.[24]
[c] Disease Severity Index (DSI) according to Medsger et al.[25]
dcSSc, diffuse cutaneous systemic sclerosis; lcSSc, limited cutaneous systemic sclerosis; ANA, antinuclear antibodies.

METHODS

Subjects

One hundred five patients with SSc (94 women and 11 men; mean age, 55.6 ± 12.6 years), who were admitted to the Clinical Immunology Unit of Sapienza University of Rome from January 2000 to December 2007, were recruited for this study. All patients fulfilled the American College of Rheumatology criteria for the diagnosis of SSc,[22] and the patients were grouped according to whether they had limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc).[23] Table 1 lists the main baseline epidemiological and clinical features of the patients. Disease activity and disease severity in SSc were measured by means the Scleroderma Disease Activity Score by Valentini et al[24] and the Disease Severity Scale by Medsger et al[25], respectively.

Ninety-six patients (81 women and 15 men; mean age, 36 ± 18 years) who fulfilled the PRP criteria[2,26] were also studied. In patients with PRP, the RP duration (mean ± SD) is 13 ± 14 years. Eighty-five healthy controls with negative test for antinuclear antibodies (73 women and 12 men; mean age 47 ± 11 years) were enrolled in this study.

All patients with SSc had been previously treated with iloprost and nifedipine, but iloprost had been discontinued at least 6 months before recruitment and nifedipine at least 2 weeks before recruitment. The majority of patients with RP had been previously treated with nifedipine, but nifedipine was discontinued at least 2 weeks before recruitment. The subjects' written consent was obtained according to the Declaration of Helsinki, and the design of the work conforms to standards currently applied in the country of origin.

Exclusion criteria included those who were unable to give informed consent, actual therapy with prostacyclin analogues and/or endothelin receptor antagonists and/or phosphodiesterase 5 inhibitors subjects with a history of uncontrolled systemic hypertension, hyperlipidemia, cardiac failure, hepatic failure, diabetics, peripheral vascular disease, coagulopathy, smokers and pregnant or breastfeeding women.

Digital Photoplethysmography

PPG was performed out using a Termoflow machine (Microlab Elettronica Sas, Pordenone, Italy). Termoflow, a computerized system, allows the simultaneous photoplethysmographic detection out of 10 fingers. Transducers fixed on the distal phalanx of each finger and insensitive to ambient light are optically calibrated to ensure uniformity of the response of the system "finger-transducer." The person who analyzed the PPG results was blinded to patient diagnosis and NVC. Baseline tracings of all digits of both hands were acquired in a quiet, air-conditioned room (24°C ± 0.4°C) when the subjects were accustomed to the room temperature after around 20 minutes. Patients and healthy controls were not allowed to drink coffee and alcoholic beverages for 2 days before the examination. The acquired photoplethysmographic curves are evaluated for morphology and amplitude of sphygmic wave. For the evaluation of pattern, the authors have used morphology and amplitude of sphygmic wave. A homogeneous pattern was defined as a pattern showing uniformity of morphology and amplitude of sphygmic wave in all 10 fingers. A dyshomogeneous pattern was characterized by different morphology in 2 or more fingers of each hand with mean variation of sphygmic wave amplitude ≥15% in 2 or more fingers of each hand. The magnitude of sphygmic wave was expressed as percentage of maximum value of sphygmic wave amplitude. This maximum value is done by constructor of Termoflow machine and is equivalent to pulsatility of brachial artery. The magnitude of sphygmic wave was calculated as mean value of magnitude of sphygmic wave of all 10 fingers of both hands.

In patients with SSc with sclerodactyly, PPG was performed only when the maximal maximum flexion of the fingers, evaluated as the point of maximum distance from the surface, was <5 mm. In fact, in our experience, the sclerodactyly with a flexion of the fingers <15 mm does not cause significant changes in the digital PPG parameters.

Nailfold Videocapillaroscopy

NVC was performed in a quiet, air-conditioned room (24 ± 0.4°C) when the subjects were accustomed to the room temperature after approximately 20 minutes. Another operator performed the NVC in each patient by using an optical probe videocapillaroscopy equipped with magnification 100× contact lens and connected to image analysis software (Pinnacle Studio, Version 8; Pinnacle Systems, Mountain View, CA).

Each subject was inside the building for a minimum of 15 minutes before the nailfold was examined at a room temperature of 20°C to 22°C. The nailfold (distal row) of the second, third, fourth and fifth finger was examined in each patient. The following capillaroscopic parameters were considered according to previous observations: presence of enlarged and giant capillaries, hemorrhages, loss of capillaries, disorganization of the microvascular array and capillary ramifications. According to Cutolo et al,[10,11] the patterns identified within the "SSc pattern" include: "early" NVC pattern: few enlarged/giant capillaries, few capillary hemorrhages, relatively well-preserved capillary distribution and no evident loss of capillaries; "active" NVC pattern: frequent giant capillaries, frequent capillary hemorrhages, moderate loss of capillaries, mild disorganization of the capillary architecture, absent or mild ramified capillaries; and "late" NVC pattern: irregular enlargement of the capillaries, few or absent giant capillaries and hemorrhages, severe loss of capillaries with extensive avascular areas, disor-