Joint Bone Spine 83 (2016) 444–447

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Concise Report

Small, medium but not large arteries are involved in digital ulcers associated with systemic sclerosis

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ARTICLE INFO

Article history:
Accepted 6 September 2015
Available online 29 December 2015

Keywords:
Systemic sclerosis
Digital ulcers
Arterial stiffness
Augmentation index
Pulse wave velocity
Applanation tonometry
Medium arteries

ABSTRACT

Objective: Digital ulcers (DU) are a burden in systemic sclerosis (SSc). Microangiopathy is a cardinal feature of SSc that plays a critical role in the development of DU. However, whether injury of medium or large vessels also contributes to DU in SSc remains controversial.
Methods: To measure concomitantly in SSc patients with and without active DU: (i) the Augmentation Index of the reflected wave (Aix_75) by radial applanation tonometry, an index of small and medium arterial function; (II) the aortic pulse wave velocity (PWV), a marker of large vessel injury (aortic stiffness).
Results: Sixty-three consecutive SSc patients were included (49 females, aged 60 [49–65] years, disease duration of 8.5 [5–13] years), including 10 (15.9%) with active DU. Patients with active DU versus those without had increased Aix_75 (35% [28–38] versus 28% [20–34], $P = 0.041$) whereas no difference existed in PWV (7.0 m/s [6.7–10.1] versus 7.6 m/s [6.8–8.7], $P = 0.887$), in systolic, diastolic, as well as aortic pulse pressure ($P = 0.126$, 0.592, and 0.161, respectively). When compared to patients in the low tertile, patients having Aix_75 in the highest tertile had 10-fold more DU (OR = 10.23; 95% CI 1.12 to 93.34, $P = 0.039$).
Conclusion: The presence of DU is associated with increased Aix_75 whereas there is no relation with PWV. These data suggest that small and medium arteries are involved in the occurrence of DU whether large vessel stiffness does not contribute. Whether Aix_75 is predictive of further DU remained to be studied.

1. Introduction

Systemic sclerosis (SSc) is a connective disease characterized by widespread vascular lesions, abnormal function of the immune system, leading to an exaggerated production of collagen and other extracellular matrix proteins [1]. Digital ulcers (DU) are highly prevalent in SSc, averaging up to 50% of SSc in some studies [2,3]. DU are responsible of local pain, functional impairment and may evolve to irreversible digital necrosis [4]. Moreover, DU may be associated with increased risk of PAH, primary myocardial involvement and even mortality [5–7]. Obliterative vasculopathy of small vessels by intima-media wall thickening followed by arterial occlusion and/or vasospasm is one of the causal factors leading to DU [8]. Macrovascular disease has also been recently documented using angio-MRI and involves digital arteries, palmar arch, and distal arteries of the arms [9]. The carotid-femoral pulse wave velocity (PWV), a marker of aortic stiffness, holds prognostic significance in various conditions, including systemic hypertension, renal failure and heart failure [10,11]. The augmentation index (Aix_75), defined as the amplitude of the reflected wave from the periphery to the heart, measured by applanation tonometry, depends on several factors including large artery but also medium and small arteries stiffness [12]. Aix_75 is also considered as an important prognostic factor of adverse events and mortality [10,11,13].

Whereas involvement is limited to small arteries, or also affect medium or large arteries has not been fully investigated and conflicting results have been reported [14–16]. The objective of the present study was to measure PWV and Aix_75 in consecutive SSc patients and to determine whether medium and large arterial functional properties are associated with the presence of active DU.

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http://dx.doi.org/10.1016/j.jbspin.2015.09.003
1297-319X/

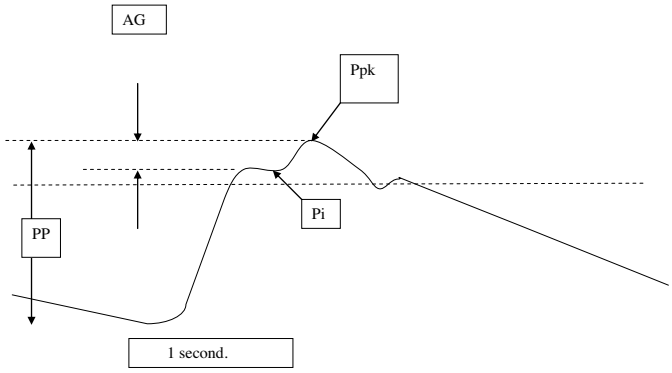
2. Methods

This study includes consecutive patients with proven SSc [17], after informed consent, followed at a tertiary institution (the Rheumatology A and Cardiology departments at Cochin Hospital, Paris, France) during a 6 months period. The protocol was approved by the local ethics committees. All patients underwent a physical examination, laboratory testing, including auto-antibodies assessments, chest computed tomography scan, pulmonary function tests [forced vital capacity (FVC) and CO diffusion capacity (DLCO)], echocardiography as part as their routine evaluation. Patients with suspected pulmonary arterial hypertension (PAH) underwent right heart catheterization (RHC) as previously reported [18,19]; PAH was defined as recommended by recent guidelines [20].

The presence of DU was defined by a painful area, ≥ 5 mm in diameter with visible depth and loss of dermis, in a location compatible with a vascular aetiology (volar surface of the digit distal to the proximal interphalangeal digital crease) and with onset of less than 3 months.

2.1. Arterial functional measurements

All measurements were performed at rest, and supine position, in an ambient temperature (> 20 °C) and quiet room. Applanation tonometry was performed as previously described [22] to determine arterial pulse waveform. Based on the radial pulse pressure wave recording that is transformed in aortic pulse waveform via a mathematical application (Mikrotip pulse high fidelity strain gauge transducer SPT 301, Millar Instruments, Inc., Houston, Tx, and Sphigmocor, PWV Medical, Ermington, Australia, 2000), we measured the height of the shoulder (Pi) of the central aortic pulse waveform and the height above the shoulder (AG) of the late systolic peak (Ppk) attributable to the reflected wave from the reflection site. We then determined the Augmentation Index (Aix in %), defined as the AG to pulse pressure (PP) ratio and it was standardized to heart rate of 75 beats-per-minute (Aix_75) (Fig. 1). Other measurements derived from applanation tonometry include systolic, diastolic and aortic pulse pressure. PWV was determined by the foot-to-foot method using two simultaneous recordings at the carotid and femoral arteries levels (Fukuda TY-306 transducers, Complior3.0) as previously described [22,23].



PP: pulse pressure.

Pi: first systolic peak.

Ppk: late systolic peak.

AG: peak due to reflected wave

Fig. 1. Applanation tonometry. PP: pulse pressure; Pi: first systolic peak; Ppk: late systolic peak; AG: peak due to reflected wave.

All measurements were performed by the same two physicians that were blinded to all other information. An average obtained from 10 cycles was selected for PWV. Aix_75 was recorded until 3–5 repetitive of the best measurements were obtained by each physicians. Values were then compared and had to be similar otherwise measurements were repeated.

2.2. Statistical analyses

The data are expressed as median [25th–75th percentile] for continuous variables, and numbers and percentages for categorical variables. SSc Patients with active DU were compared to those without using Mann-Whitney test for comparisons of continuous variables, and Chi^2 or Fisher's exact test for differences in frequency as appropriate. Spearman correlations tests detected the presence of correlations between variables. A P-value < 0.05 was considered statistically significant. The STATA statistical software, version 10.1 (StataCorp LP, College Station, TX) was used for all data analysis.

3. Results

3.1. Patient characteristics

A total of 63 SSc patients (age 60 [49–65] years, disease duration 8.5 [5–13] years) were included. Tables 1 and 2 represent the baseline characteristics, echo, PWV and applanation tonometry in the whole cohort and in those with versus without active DU. As expected, more patients with active DU were treated with endothelin antagonists (40.0% vs. 5.7%; $P = 0.010$). NT-proBNP concentration was 104 ng/L (39–184) in the subgroup of SSc with DU versus 70 ng/L (28–154) in those without ($P = 0.540$); 20% (2) and 28% (15) of SSc patients had elevated NT-proBNP > 125 ng/L, respectively ($P = 0.630$).

3.2. Applanation tonometry and PWV measurements

Aix_75 correlated with age ($r = 0.309$, $P = 0.016$) and NT-proBNP ($r = 0.412$, $P = 0.002$) whereas PWV correlated with age ($r = 0.518$, $P < 0.001$) but not with NT-proBNP ($P = 0.172$). There was no difference in Aix_75 and PWV between patients with NT-proBNP > 125 ng/L versus those with NT-proBNP < 125 ng/L ($P = 0.690$ and $P = 0.261$, respectively), and between those treated or not with steroids ($P = 0.392$). SSc patients with DU versus those without had increased Aix_75 (35% [28–38] versus 28% [20–34], respectively, $P = 0.041$) while there was no difference in PWV (7.0 m/s vs. 7.6 m/s, respectively; $P = 0.887$).

Patients were divided into three tertiles based on Aix_75 value: tertile 1 for Aix_75 $\leq$ 25%, tertile 2 included patients with Aix_75 from 26% to 32%, and tertile 3 for patients having Aix_75 $\geq$ 33%. The presence of DU was 10-fold more prevalent in SSc patients having Aix_75 in the highest tertile versus in the lowest tertile (OR = 10.23; 95% CI 1.12 to 93.34, $P = 0.039$).

3.3. Subgroup of patients with proven pulmonary arterial hypertension (PAH)

Right heart catheterization was performed in 11 (17.4%) patients because of sPAP > 40 mmHg by echocardiography in 8, DLCO/predicted < 55% in 7 or unexplained dyspnea in 2. PAH was confirmed in 6 (9%) patients of the cohort. Patients with PAH were older than those free of PAH, had increased aortic systolic and pulse pressure, elevated NT-proBNP concentrations (data not shown); none had active DU.