Microvascular Research 114 (2017) 46–51

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

Nailfold capillaroscopic changes in patients with idiopathic pulmonary arterial hypertension and systemic sclerosis-related pulmonary arterial hypertension

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ARTICLE INFO

Article history:
Received 7 April 2017
Revised 10 May 2017
Accepted 9 June 2017
Available online 12 June 2017

Keywords:
Capillaroscopy
Pulmonary arterial hypertension
Systemic sclerosis

ABSTRACT

Pulmonary arterial hypertension (PAH) represents one of the main clinical expressions of the vascular changes in systemic sclerosis (SSc). Lung microvascular changes can play a role in the pathogenesis of idiopathic PAH (IPAH) also. The aim of this study is to investigate the presence of capillaroscopic abnormalities in patients with IPAH and to evaluate the differences in capillary nailfold changes between patients with IPAH and patients with SSc with and without PAH.

Methods: 39 SSc patients (19 with PAH – SSc-PAH and 20 without – SSc-noPAH), 21 subjects with IPAH and 20 healthy subjects were recruited. PAH was diagnosed by right heart catheterization. Nailfold videocapillaroscopy was performed (NVC) in all recruited subjects; capillary quantitative parameters (loops length and width, capillary density, neoangiogenesis) were evaluated and a semiquantitative scoring was used (normal, minor or major abnormalities for healthy controls and IPAH subjects and specific patterns – early, active and late – for SSc subjects) to define microvascular alterations.

Results: The presence of capillaroscopic abnormalities was detected in 38,1% subjects with IPAH; particularly, compared to healthy controls, capillary density was significantly lower (7,5 ± 1,65 loops/mm vs 9 ± 1,37 loops/mm $p < 0,05$) and mean capillary width was significantly higher (21 ± 13 μm vs 17 ± 3 μm $p < 0,05$). A more severe NVC pattern (active/late) was described. SSc-PAH patients compared to SSc-noPAH patients (73,2% vs 50% respectively, $p < 0,05$), with a significantly lower capillary density (5,64 ± 1,9 loops/mm vs 6,5 ± 1,3 loops/mm $p < 0,05$) and a significantly higher capillary width (55 ± 7 μm vs 35 ± 8 μm - $p < 0,05$) and mean number of neoangiogenesis (N/mm) (1 ± 0,33 vs 0,2 ± 0,22 respectively $p < 0,05$).

Conclusions: These data, beyond to confirm the role of microvascular damage in SSc-related PAH, support the hypothesis of systemic microvascular involvement in IPAH also, which can be detected by NVC, although further studies are needed to establish whether the changes in the systemic microcirculation are causal or consequential to PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a disorder which may be associated with a wide range of conditions, including connective tissue diseases (Galiè et al., 2016).

Systemic sclerosis (SSc) is an autoimmune connective tissue disease (CTD) characterized by vasculopathy and progressive fibrosis of the skin and visceral organs (gastrointestinal tract, heart, kidneys and lungs). Vascular involvement in systemic sclerosis includes Raynaud's phenomenon (RP) and digital ischemia, telangiectasias, gastric antral vascular ectasia, scleroderma renal crisis and pulmonary arterial hypertension (PAH), which is one of the most severe organ complications and a leading cause of death (Ghrénassia et al., 2014; Michelfelder et al., 2017). PAH is a clinical condition that falls under WHO group 1 of pulmonary hypertension classification which includes idiopathic PAH (IPAH), heritable (HPAH), PAH due to drugs and toxins, or PAH associate to other diseases including CTDs. The most frequent form of PAH belonging to Group 1 is represented by IPAH followed by PAH associated to CTDs; particularly PAH associated to SSc (SSc-PAH) is the most significant both in terms of prevalence and in terms of poor prognosis compared

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http://dx.doi.org/10.1016/j.mvr.2017.06.005
0026-2862/

to the other CTDs. IPAH and SSc-PAH share many histopathological aspects; particularly vascular changes play key a role in both forms. Pathologic lesions of PAH affect the whole pulmonary circulation, particularly the distal pulmonary arteries. The pulmonary vasculature in PAH is characterized by medial hypertrophy, intimal proliferative/fibrotic changes, adventitial thickening with moderate perivascular inflammatory infiltrates, in situ thrombotic lesions, and plexiform lesions (Hassoun et al., 2009). Further, idiopathic PAH and SSc-PAH share other pathogenic features such as the endothelial dysfunction, in particular the increment of endothelin levels and fibrosis which causes vascular remodelling, vasoconstriction and thrombosis (Dababneh et al., 2014; Peled et al., 2008).

Nailfold video-capillaroscopy (NVC) is a non-invasive diagnostic tool that is essential in the diagnosis of CTDs, and particularly in SSc; it permits the detection of local microvascular changes in SSc, which are an expression of the systemic vascular changes characteristic of the disease, even in the very early stage of disease, often before the systemic manifestations appear (Cutolo et al., 2005; Smith et al., 2016a; Ingegnoli et al., 2015; Ingegnoli et al., 2013a; Ingegnoli et al., 2013b).

The aim of this study was to investigate presence of periungual NVC abnormalities in patients with IPAH and to evaluate the differences in various capillaroscopic parameters compared to patients affected by SSc with and without PAH, in order to evaluate if these microvascular alterations might be related to immunological changes or specific clinical features.

2. Patients and methods

We evaluated 20 consecutive SSc patients (19F, 1 M mean age 48,1 ± 6,8, range 42–60) without PAH (SSc-noPAH), 19 consecutive patients with SSc associated PAH (SSc-PAH) (17 F, 2 M mean age 55,8 ± 11,4 range 39–65) 21 patients with IPAH (14 F 7 M, mean age 58,2 ± 3,8, range 45–63) and 25 healthy subjects as control group (20 F, 5 M, mean age 45,4 ± 8,1 range 39–65). All patients with SSc fulfilled the ACR/EULAR 2013 diagnostic criteria for SSc (van den Hoogen et al., 2013). The diagnosis of PAH was performed by right heart catheterization (RHC) and defined as mean pulmonary arterial pressure ≥ 25 mm Hg with pulmonary artery wedge pressure (PAWP) of ≤15 mm Hg and increased pulmonary vascular resistance (PVR) >3 WU.

All patients with SSc and patients with IPAH underwent lung functional tests with CO diffusing capacity measurement (DLco), 6 minute walking test, chest x-ray, pulmonary high resolution computed tomography (HRTC), to assess the presence and the extent of interstitial lung disease. In SSc patients, the modified Rodnan skin score (mRSS) (Kahaled et al., 1986) the presence/absence of RP, digital pitting scars, telangiectasia and calcinosis were evaluated, as well as the presence of extra-pulmonary clinical manifestations and laboratory tests to detect anti-nuclear antibodies (ANA), anti-centromeric antibodies (ACAs) and anti-Extractable Nuclear Antigens (anti-ENA), including anti-Topoisomerase I (anti Scl-70) autoantibodies, C3 and C4 complement fractions, full blood count and renal function.

NVC was performed on all recruited healthy subjects and patients, none of which were in an acute phase of pulmonary disease. Patients suffering from peripheral microangiopathies, such as diabetes, which could potentially modify the capillaroscopic findings were excluded. All tests were performed and subsequently analysed by two independent observers who had no knowledge of the diagnosis.

Appropriate informed consent was obtained from each patients and the study was approved by Institutional Ethics Committee.

2.1. Capillaroscopy technique and image analysis

NVC was performed at room temperature (between 23° and 25 °C) with the patient in a sitting position and the hand being examined placed at heart level. One drop of immersion oil was applied to the nailfold to maximise the translucency of the keratin layer. Capillary tests were performed on all fingers of both hands, excluding thumbs, and greater attention was paid to the ring finger of the non-dominant hand as this offers the best capillary visibility, as previously described (Corrado et al., 2010). NVC was performed using a computerised video-capillaroscopy system with a fibre optic probe magnified by 200× (*HORUS*). Images were subsequently captured, coded, saved and analysed later by two independent observers.

For each capillaroscopic image the following parameters were evaluated: linear capillary density (capillary number/mm), capillary length (evaluated by measuring capillaries of the distal row from base to apex), presence of micro-haemorrhages, capillary disarrangement and neoangiogenic aspect defined as bushy, bizarre shaped loops (originating from a single normal sized capillary)/mm. The morphology of tortuous loops was considered as normal or abnormal according to EULAR definition (Smith et al., 2016a, 2016b). The capillary width, expressed in μm, was evaluated by measuring the diameter of capillary afferent limb, capillary efferent limb and capillary apex and considering the capillary width as the width of the capillary loop at its widest section (Etehad Tavakol et al., 2015). We consider as ectasia capillaries with width ranging from 20 to 50 μm and as megacapillaries the capillaries with width ≥50 μm (Ingegnoli et al., 2009). Capillary absolute number was obtained counting all capillary loops, observable in the first row, in 1 mm per field, over 8 fingers, 4 fields per finger, as previously described (Trombetta et al., 2016). The overall capillaroscopic patterns were defined as normal (6–8 capillaries/mm, capillary length between 200 and 500 μ, hairpin-shaped loops arranged in parallel rows, absence of haemorrhages), minor abnormalities (6–8 capillaries/mm, <50% tortuous loops, arranged in parallel rows, with no haemorrhages), major abnormalities (normal or decreased capillary density, >50% tortuous, enlarged loops, disarranged, with haemorrhages), scleroderma pattern (decreased number of capillaries, tortuous, branched, bushy, enlarged, giant, disarranged, with haemorrhages) (Ingegnoli et al., 2005; Ingegnoli et al., 2013c). For systemic sclerosis patients, the capillaroscopic scleroderma patterns were defined as early, active or late, according to classification of Cutolo (Cutolo et al., 2000).

2.2. Statistical analysis

The reproducibility of semi-quantitative parameters was evaluated by measuring agreement between the two independent observers using Cohen's kappa coefficient, with a value of 0.80 indicating a good inter-observer agreement in the overall evaluation of capillaroscopic findings. Results for each quantitative capillaroscopic parameter (density, length, width, number of bush capillaries, number of microhaemorrages) were expressed as mean ± SD. Semi-quantitative parameters were expressed as percentage. To detect differences between the four groups the Kruskal-Wallis non-parametric test was used for quantitative parameters. The χ^2 test was used for semi-quantitative parameters, when applicable, with Fischer correction if required. A p value ≤0.05 was considered significant.

3. Results

3.1. Clinical and laboratory findings

All groups were matched for age; no difference in mean disease duration (PAH) was found between SSc-PAH and IPAH patients, whereas mean duration of SSc was significantly higher in patients without PAH compared to those with PAH. Reduced PaO_2 at rest was not observed in both IPAH patients and SSc-patients (with and without PAH), but a severe reduction in all patients in all three groups was induced by minimal exercise in a 6 minute walking test. In all SSc patients, ANA were detected at various concentration titres; particularly, anticentromere antibodies were found in 73,6% and 20% of patients with SSc-PAH and SSc-no PAH, respectively, whereas anti-Topoisomerase antibodies were found in 26,3% of SSc-PAH subjects and in 80% of Sc-noPAH