Nailfold videocapillaroscopy in primary antiphospholipid syndrome (PAPS)

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Objectives. To evaluate microcirculatory changes (functional and morphological) in primary antiphospholipid syndrome (PAPS) patients.

Methods. Thirty-one patients were examined using nailfold videocapillaroscopy (18 PAPS patients and 13 healthy subjects). The patients were subdivided into two subgroups, with lupus anticoagulant (n=8) and with anticardiolipin (n=10) antibodies. Capillary morphology was determined; diameters (µm) and functional capillary density (FCD, number capillaries/mm²) were measured in control conditions. Blood flow velocity (CBFV, mm/s) was also evaluated at rest and after release of 60 s arterial occlusion.

Results. The percentage of subjects with at least one morphological alteration in the observed capillaries was 77.8% for patients and 21.3% for healthy subjects. Capillary diameters (µm) [afferent (AD), apical (APD) and efferent (ED)] were significantly smaller (mean ± s.d.; AD-PAPS, 7.4 ± 2.1; control, 9.1 ± 2.6, P=0.063; APD-PAPS, 11.6 ± 2.3; control, 14.4 ± 3.8, P=0.015; ED-PAPS, 8.4 ± 2.0; control, 10.9 ± 3.2, P=0.011) in PAPS patients compared with controls. CFD (PAPS, 8.5 ± 3.2; control, 8.3 ± 2.9, P=0.862), mean resting CBFV (PAPS, 0.73 ± 0.31; control, 0.88 ± 0.41, P=0.278), mean peak CBFV after occlusion (PAPS, 1.07 ± 0.52; control, 1.59 ± 0.91, P=0.063) and mean time (s) to reach it (PAPS, 5.2 ± 1.7; control, 4.6 ± 1.8, P=0.101) were not statistically different between the two groups.

Conclusion. Our results suggest that nailfold capillary morphology is altered in patients with PAPS, but these changes could not be correlated to impairment of functional parameters.

Key words: Antiphospholipid syndrome, Videocapillaroscopy, Reactive hyperaemia, Nailfold capillaries.

Antiphospholipid syndrome (APS) is characterized by recurrent thrombosis (venous or arterial) and/or miscarriages in patients with antiphospholipid antibodies (aPL) [1, 2]. APS can occur alone (primary APS, PAPS) or in association with autoimmune diseases (secondary APS, SAPS), systemic lupus erythematosus (SLE) being the most frequent [3, 4]. The vascular lesions of the disease are associated with non-inflammatory vasculopathy [5]. The aPL can be detected by lupus anticoagulant (LA) and anticardiolipin (aCL) antibody assays in immunological tests [6].

Nailfold videocapillaroscopy is a non-invasive test that allows direct observation of the microcirculation in cutaneous capillaries [7–9]. Microvascular abnormalities have been described in scleroderma [10], SLE [11], Sjögren’s syndrome [12] and other rheumatic diseases.

Our aims were to study microvascular morphology and haemodynamic changes in the nailfold capillaries in healthy volunteers and PAPS patients. Capillary morphology, density, red blood cell velocity at rest and after a period of tissue ischaemia (the post-occlusive reactive hyperaemia response) [13] were determined. We used subgroups of PAPS patients to assess the influence of LA and aCL on the development of functional microangiopathy.

Patients and methods

This was a controlled clinical study, evaluating 31 individuals paired by sex and age, divided into two groups: 18 PAPS patients and 13 controls. The PAPS group was further divided into two subgroups: LA (eight patients, independently of the presence of aCL) and aCL [10 patients with aCL immunoglobulin (Ig) G > 20 GPL and/or IgM > 20 MPL]. All individuals signed a consent form and the protocol was approved by the Ethics Committee of the State University of Rio de Janeiro.

PAPS was diagnosed from a history of venous and/or arterial thrombosis, confirmed by imaging or Doppler, and/or repeated miscarriages, associated with two determinations of aPL (aCL and LA), with a minimum interval of 6 weeks. We excluded smokers and persons with other autoimmune diseases, AIDS, hepatitis C, diabetes mellitus, hypertension, alcoholism, dyslipidaemia or other factors that could change blood viscosity. Due to the risk of new thrombotic episodes and/or undesirable symptoms, no change of prescribed medication was allowed.

Due to skin pigmentation, in each group 60% of all subjects were rejected, as reported earlier [14].

All subjects were acclimatized for 30 min in a room kept at 24 ± 1 °C before the examination. They were seated in a chair with the left arm at heart level and their blood pressure was measured using the standard auscultatory method. The fourth finger was supported on an acrylic base, 2 cm above palm level, mounted on the x–y stage of a three-eyepiece Leica DMLM microscope (Wetzlar, Germany), equipped with epi-illumination (100 W xenon lamp) and a closed-circuit TV system. Skin temperature was controlled with a YSI Precision 4000A digital thermometer (Dayton, OH, USA) with the probe taped within 1 cm proximal to the nailfold.

A drop of mineral oil was spread over the observation site to improve image quality. The entire nailfold bed was observed...
The functional capillary density was determined as the number of capillaries/mm² with flowing red blood cells, and the morphology was evaluated according to Gibson et al. [15]. Capillary loop diameters, afferent (AD), apical (APD) and efferent (ED), were also assessed.

For measurements of capillary blood flow velocity (CBFV), a pressure cuff (1 cm wide) was placed around the proximal phalanx and connected to a mercury manometer. Resting values of CBFV were obtained for at least 1 min before the cuff was inflated above systolic pressure for 1 min. The peak increase in CBFV above rest and the time taken to reach it were measured [13]. Measures were obtained using the software CapImage [16].

Results are presented as mean ± s.d. The parametric Student’s t test and the non-parametric Mann–Whitney test were used, both with P < 0.05 indicating statistical significance.

Results
Mean age (yr) was 30.2 ± 6.3 for patients and 34.5 ± 7.3 for controls, and median PAPS time since diagnosis was 2.5 yr. Arterial thrombosis, independent of venous thrombosis and/or fetal loss, was present in eight patients (44.4%). No patient showed Raynaud’s syndrome during the examination. Patients were using oral anticoagulant (warfarin, almost 80%) and/or aspirin (100 mg/day, 27.8%).

Capillary diameters (μm) [afferent (AD), apical (APD) and efferent (ED)] were significantly smaller in PAPS patients compared with controls (AD-PAPS, 7.4 ± 2.1; control, 9.1 ± 2.6, P = 0.063; APD-PAPS, 11.6 ± 2.3; control, 14.4 ± 3.8, P = 0.015; ED-PAPS, 8.4 ± 2.0; control, 10.9 ± 3.2, P = 0.011) (Fig. 1). There were also differences in capillary diameter between LA and aCL patients (Fig. 1).

Functional capillary density (number of capillaries/mm²) (PAPS, 8.5 ± 3.2; control, 8.3 ± 2.9, P = 0.862), mean resting CBFV (mm/s) (PAPS, 0.73 ± 0.31; control, 0.88 ± 0.41, P = 0.278), mean peak CBFV after occlusion (mm/s) (PAPS, 1.07 ± 0.52; control, 1.59 ± 0.91, P = 0.063) and mean time to reach it (s) (PAPS, 5.2 ± 1.7; control, 4.6 ± 1.8, P = 0.101) were not different between the two groups.

Haemorrhages or deposits of haemosiderin were not observed. Morphological alterations (apical cobling, one crossing between loops with moderate cobling and dual crossing between loops) were observed in 14 out of 18 PAPS patients (77.8%) and in three out of 13 controls (21.3%). Bushy capillaries or one crossing in the same capillary loop were only found in PAPS patients.

Discussion
This study evaluated morphological and functional alterations of the microcirculation in PAPS. FCD, one of the main functional parameters, was not different between the groups and subgroups, suggesting similar perfusion in patients and controls.

Regarding red blood cell velocities and time to reach peak velocity, there was no difference between PAPS patients and controls or between LA and aCL subjects. In the morphological evaluation, however, differences were found in the apical and efferent diameters between the PAPS and control groups, with smaller diameters in PAPS patients. Diameters were measured as the width of the red blood cell column because the capillary wall was not visible. Since average red blood cell velocity was similar in patients and controls, and diameters were smaller in patients than in controls, lower quantities of red blood cells and therefore smaller amounts of O₂ were available to the tissue surrounding these capillaries in patients. In the subgroups LA and aCL, apical capillary diameter was smaller in LA patients, suggesting an impairment of the circulation in this region.

At least one unspecified morphological alteration was found in 14 patients (77.8%). Morphological changes in capillaries of 13 patients with aPL, eight with PAPS and five with SAPS (APS + SLE), with loop dilation in both PAPS (63%) and SAPS (100%), have been described [17]. This study had no control group and did not specify the region of the loop in which the dilation occurred. In a case–control study (n = 66) in aCL patients with isotype IgG, a high incidence of capillary morphological abnormalities was reported in both groups (70% in patients and 78% in controls) [18], but only two patients (6.1%) with aPL and 10 controls (30.3%) had capillary dilation. In the present study, only the presence of aCL was taken into account and individuals without any autoimmune disease were included. The greater prevalence of digital gangrene in the control group (30 vs 6%, P = 0.02) suggests that these patients, despite the absence of aPL, could have worse vascular disease than the other group.

A recent case-control study [19] evaluated the association of morphological abnormalities and the presence of aPL, separated according to IgG/IgM concentrations, in patients with rheumatic diseases (SLE, PAPS, undifferentiated connective tissue disease) or Raynaud’s disease. No morphological changes were observed, but capillary haemorrhages and haemosiderin deposits were seen (53.3%), with a higher incidence in IgG+IgM+ patients (75%). Pericapillary deposits of haemosiderin or haemorrhages were not found in our study.

In previous studies [17, 18], morphological changes were observed. In our study, we found at least one unspecified alteration in 77.8% patients compared to 23.1% controls without any significant blood flow impairment. Perhaps the anticoagulant treatment used by 80% of the patient group accounts, at least in part, for these findings.

Our results showed a higher incidence of morphological changes in nailfold capillaries of PAPS patients compared with controls, without significant impairment of functional parameters.

Acknowledgements
The authors wish to thank Dr Roger Levy for sending us the patients and Mr Fabiano Albuquerque for reading the tapes. The work was supported by the National Research Council (CNPq grant number 521850/96-7).

The authors have declared no conflicts of interest.

References