

Ultrasound classification of finger pulp blood flow in patients with systemic sclerosis: A pilot study

Alain Lescoat, François Robin, Nicolas Belhomme, Alice Ballerie, Marine de Saint Riquier, Martine Sebillot, Jean-David Albert, Thomas Le Gallou, Aleth Perdriger, Jégo Patrick, et al.

▶ **To cite this version:**

Alain Lescoat, François Robin, Nicolas Belhomme, Alice Ballerie, Marine de Saint Riquier, et al.. Ultrasound classification of finger pulp blood flow in patients with systemic sclerosis: A pilot study. Arthritis Care and Research, 2023, 75 (2), pp.299-306. 10.1002/acr.24779 . hal-03359414

HAL Id: hal-03359414
https://hal.science/hal-03359414

Submitted on 15 Oct 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NoDerivatives| 4.0 International License

DR. ALAIN LESCOAT (Orcid ID : 0000-0003-2081-8558)
DR. FRANÇOIS ROBIN (Orcid ID : 0000-0001-5134-8160)
DR. GUILLAUME COIFFIER (Orcid ID : 0000-0003-3560-128X)

Article type : Original Article

ULTRASOUND CLASSIFICATION OF FINGER PULP BLOOD FLOW IN PATIENTS WITH SYSTEMIC SCLEROSIS: A PILOT STUDY

Alain Lescoat[1,2] MD PhD, François Robin[3,4] MD, Nicolas Belhomme[1,2] MD, Alice Ballerie[1,2] MD, Marine de Saint Riquier[3] MD, Martine Sebillot[1] MD, Jean-David Albert[3,4] MD, Thomas Le Gallou[1] MD, Aleth Perdriger[3] MD PhD, Patrick Jégo[1,2] MD PhD, Guillaume Coiffier[1,5*] MD, Claire Cazalets[1*] MD

1- *Department of Internal Medicine and Clinical Immunology, CHU Rennes, Univ Rennes, France*
2- *Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) – UMR_S 1085, F-35000 Rennes, France*
3- *Department of Rheumatology, CHU Rennes, Univ Rennes, France*
4- *INSERM, Univ Rennes, INRA, CHU Rennes, Institut NUMECAN (Nutrition Metabolisms and Cancer), F-35033 Rennes, France.*
5- *Department of Rheumatology, CH Dinan, France*

**Equal contribution*

Word count: 3300/3800 words ; 2 tables, 3 Figures ; 43 references; 2 supplementary Figures.

Running heading: *SSc and Finger Pulp Blood Flow*

Corresponding author: Alain Lescoat
Department of Internal Medicine & Clinical Immunology, CHU Rennes, South Hospital, 16 bvd de Bulgarie - 35203

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ACR.24779

Accepted Article

RENNES Cedex 2 - BP 90347
E-Mail : alain.lescoat@chu-rennes.fr
Phone: +33 2 99 26 71 28 fax : +33 2 99 26 71 98

Financial disclosures:

A Lescoat, G Coiffier, C Cazalets, N Belhomme, A Ballerie, M De Saint Riquier, A Perdriger, F Robin, Martine Sebillot, Jean-David Albert, Thomas Le Gallou, P Jégo report no conflict of interest.

Funding statement: This study did not receive any financial support

Authors' contributions:

A Lescoat & G Coiffier wrote the first draft of the manuscript, G Coiffier & A Lescoat performed the statistical analyses, C Cazalets designed the classification, C Cazalets, A Ballerie, F Robin, M Sebillot, N Belhomme, G Coiffier, M De Saint Riquier, A Perdriger, P Jégo, A Lescoat, T Le Gallou, JD Albert designed the study, corrected and added substantial modifications to the manuscript.

Accepted Article

Abstract (238/250 words):

Objectives: To define a semi-quantitative classification of FPBF and to evaluate whether this classification could be used to assess FPBF in healthy controls and in SSc patients.

Methods: 30 controls and 86 SSc patients were consecutively included. A classification of FPBF including 5 grades (from grade 0 (No signal) to 4 (signal detected on the entire finger pulp, including the sub-epidermal vascular network) was evaluated. This classification was explored in basal conditions and after hand baths in hot and cold water in controls. Its relevance was also assessed at room temperature in SSc patients.

Results: In controls, PDUS FPBF was improved after hot challenge ($p=0.024$), whereas cold challenge decreased FPBF ($p=0.001$). FPBF correlated with the vasodilation status assessed by the resistivity index of radial arteries ($R=-0.50$, $P=0.0049$). Grade 0 was more frequent in SSc patients than in controls (22.1% versus 3.3% ($p<0.05$)). In SSc patients, Grade 0 was associated with severity markers of the digital vasculopathy such as digital ulcers (DU) (current or past) ($p<0.05$) or ulnar artery occlusion ($p<0.05$). On the contrary DU were less frequent in patients with Grade 4 ($p<0.05$). A pathological threshold of less than 2 (grade 0 or 1) was significantly associated with DU (OR=6.67, IC95% (2.31-19.21), $p<0.0001$).

Conclusions: PDUS allowed a semi-quantitative evaluation of FBPF in SSc and controls. Further studies are warranted to validate these results in independent SSc populations and to compare PDUS to existing tools assessing digital blood flow.

Keywords: Ultra-sound, Doppler, systemic sclerosis, scleroderma, digital ulcers, finger pulp

Significance and Innovation:

1-Power Doppler Ultrasound (PDUS) allows a semi-quantitative visual evaluation of Finger Pulp Blood Flow (FPBF).

2- Impaired FPBF assessed by PDUS may reflect the severity of digital vasculopathy in patient with SSc.

Accepted Article

3-Severe alteration of FPBF is associated with digital ulcers or macrovascular involvement such as ulnar artery occlusion.

Accepted Article

Accepted Article

INTRODUCTION

Endothelial dysfunction is a hallmark of Systemic sclerosis (SSc) (1,2). The main manifestations related to SSc-vasculopathy are Raynaud's phenomenon (RP) and digital ulcers (DUs) (3–6). DUs are classically localized on the fingertips and are responsible for high morbidity with detrimental impact on hand functioning (4,7,8). These digital manifestations could be the direct result of decreased finger-pulp blood flow (FPBF) due to SSc-related obliteration of micro-vessels (9–12). Macrovascular disease secondary to obliterating endothelial proliferation has also been described in SSc (11). Ulnar artery may be especially involved as almost 25% of SSc patients have ulnar artery occlusion (12–16). The current standard of care of SSc vasculopathy is based on vasodilator treatments but new accessible and reliable imaging outcome measures assessing the impact of such therapies on FPBF are still needed (9,17,18). Recent studies have suggested that PDUS assessment of FPBF could be an interesting tool to assess the impact of IV iloprost on digital vascularization (9). Nonetheless, to date, there is no standardized classification of FPBF in SSc and the relevant definition of a pathological FPBF is yet to be determined.

Recent studies have proposed a semi-quantitative classification of FPBF based on the surface of positive Doppler signal of the finger pulp regardless of the signal localization in the pulp, but an approach grounded on anatomic considerations might also be relevant (12). The vascular supply of the finger pulp is derived from the proper digital pulp artery which is prolonged by perforating branches. These perforating branches follow collagen fiber cords which bind the periosteum of the distal phalanx and the epidermal basement membrane (19). The perforating branches of the proper digital pulp artery secondly anastomose in a sub-epidermal superficial terminal network. As microangiopathy is the early hallmark of SSc, the first damaged vessels in SSc-vasculopathy could be the small vessels from this sub-epidermal superficial network. This may explain that DU are preferentially localized on fingertips. A classification of FPBF based on this anatomical hypothesis and exploring the localization of doppler signal in the pulp may better reflect the disease process.

The objectives of this observational study were to define a semi-quantitative classification of FPBF based on such an anatomical rationale and to evaluate whether this classification is relevant to assess FPBF in healthy controls and in SSc patients.

METHODS

1/ Patients

Patients with SSc fulfilling the 2013 ACR/EULAR classification criteria were consecutively

recruited at the departments of Rheumatology and Internal Medicine of Rennes University Hospital (20). Non-SSc controls subjects were recruited from the medical staff of these departments. The ethics committee of Rennes University Hospital approved this cross-sectional observational study as a sub-analysis of previous studies (approvals 14.53 and 15.09). The study complied with the recommendations of the Declaration of Helsinki. Informed consent of all patients was obtained prior to investigations.

2/ Clinical parameters

At inclusion, demographic data, SSc history, cutaneous subsets (diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc)) and disease duration since the date of the first non-RP symptom were collected for each patient (21). Autoantibodies, current or previous use of vasodilator drugs (sildenafil, bosentan, history of IV iloprost) or calcium channel blockers (CCB) were evaluated at the time of PDUS evaluation. No patient with ongoing IV iloprost was included in the study to avoid direct interaction with PDUS results (9). The following clinical data were also collected for all patients on the day of PDUS evaluation: modified Rodnan skin score (mRSS), presence of active DU. The previous history of ischemic DUs was based on medical records. Capillaroscopic findings were also evaluate based on dermoscopic evaluation of the third finger.

3/ PDUS settings

This study is based on an adapted protocol presented in a pilot study previously published by our group in Arthritis Care & Research and used by others in studies published in this same journal (11,12,17). The investigator performing PDUS evaluations was blinded for the results of clinical and serological parameters. PDUS evaluation was conducted after 15 minutes of acclimatization in our US laboratory. A MyLab Class C (ESAOTE, Florence, Italy, 2013) ultrasound device was used with a 6-18 MHz linear array transducer. B-mode and PD machine settings were standardized as follows: B-mode frequency of 18 MHz, B-mode gain of 50-60%, Doppler frequency of 10 MHz, Doppler gain of 50-60%, low wall filters, and pulse repetition frequency (PRF) of 750 Hz, depending on the depth of the considered anatomic area (22). The same rheumatologist (GC) with a 10-year experience in musculoskeletal and SSc ultrasound performed all PDUS examinations. As this study was conducted in pragmatic conditions, patients could be scheduled at different hours of the day but all PDUS were performed in the same room with an ambient temperature from 19 to 22°C.

4/ PDUS parameters

Step 1-Diagnosis of ulnar artery occlusion (UAO): Ulnar artery blood flow was measured

Accepted Article

using a palmar transverse view of the Guyon canal including the Pisiform bone. UAO was defined as a complete abolition of blood flow assessed by PDUS (13). An Allen test was also performed during PDUS evaluation and UAO was confirmed when no PDUS signal was detected in the commissural artery between finger II and III, when radial artery was temporarily compressed by the examiner.

Step 2- Measurement of radial artery Resistive Index (RI): radial artery RI was assessed using a palmar longitudinal view of radial artery proximal to its entry in the anatomical snuffbox. RI was calculated using PDUS spectral analysis as followed: RI = (Peak systolic velocity-Lowest diastolic velocity) / Peak systolic velocity. We tested the hypothesis that high RIs reflected a higher level of downstream collateral resistance, secondary to a defect in vasodilation or occlusion of distal arterioles or capillaries (10). RI provided an objective measure of vasodilation status after exposure to various temperatures (**Supplementary Figure 1A, B**).

Step 3- Evaluation of FPBF: A standardized US evaluation of the FPBF on the third and fourth fingers of both hands was performed. FPBF was assessed using a longitudinal palmar view of the third phalanx (**Figure 1A**). No pressure was applied on the finger pulp as FPBF was evaluated. FPBF was assessed in the absence of the ischemic phase of Raynaud's phenomenon. Instead of a classification of FPBF based on the surface of the positive Doppler signal of the entire finger pulp, we proposed a classification based on the depth of positive Doppler signal on a longitudinal view of the finger pulp (17).

FPBF was classified into 5 grades (grade 4 to grade 0) as illustrated in **Figure 1B**. As this classification was meant to be feasible in daily practice, we based FPBF evaluation on a visual analysis of the doppler signal of the finger-pulp and not on an automatic grading system. The evaluation of the inter and intra-observer agreement of this visual reading was among the objectives of this study.

The 5 grades of this classification were based on anatomic considerations and defined as follows (19): in grade 4, a continuous positive Doppler signal was recorded in the sub-epidermal region of the finger pulp reflecting a dense preserved and vasodilated sub-epidermal superficial terminal network. Grade 3 was defined in case of discontinuation of the Doppler signal in the sub-epidermal region of the finger pulp. Grade 2 was defined by the absence of any Doppler signal in the sub-epidermal region with a Doppler signal only detected in perforating arteries of the finger pulp and in the proper digital artery. Grade 1 was defined when the Doppler signal was only detected in the proper digital artery. Grade 0 was defined when no Doppler signal could be detected in the entire finger pulp. Using this method, vascular evaluation including assessment of UAO, FPBF and RI was performed in 10 minutes, even in patients with digital flexion ankylosis (23).

Accepted Article

Accepted Article

4/ Study design and dynamic vascular evaluation in non-SSc controls.

Evaluation of UAO, FPBF and RI were performed in controls in baseline conditions, and repeated for FPBF and RI evaluations after immersing each hand one minute in a warm bath (38°C), and repeated a third time after immersing each hand in a cold bath (15°C).

Due to ethics considerations (approvals 14.53 and 15.09) evaluation of UAO, FPBF and RI were performed in patients with SSc only at room temperature.

5/ Statistical analysis

Quantitative variables were expressed as median ± interquartile range (IQR) or mean (±SD) depending on Gaussian distribution according to Kolmogorov-Smirnov's test. These variables were analyzed using Mann & Whitney's non-parametric U test or Student's t-test depending on Gaussian distribution. Association between qualitative variables were evaluated by the Chi-square test (χ^2) or Ficher's exact test and expressed with Odds Ratio (OR) and 95% Confidence Intervals (CI), a Bonferroni post hoc test was performed for multiple comparisons.

Correlations were assessed using Spearman R coefficients. The sign of the R showed the direction of the correlation, a negative R meaning that the variables are inversely related. The strength of the correlation increased both from 0 to +1, or 0 to −1, with 0.40 – 0.59 considered as a "moderate" correlation, 0.60 – 0.79 as "strong" and 0.80 – 1 as "very strong".

Inter-observer Kappa coefficients were based on a separate reading of all images by two independent readers (AL and GC) (24). Intra-observer Kappa coefficients were based on a separate reading of all images by the same readers 3 months later, blinded from their previous evaluations. As GC performed all PDUS evaluations, his first reading was considered for analysis, to reflect real-life conditions. Kappa coefficients were interpreted as follows: values ≤ 0 as indicated no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement (24). Statistical analyses were performed using SPSS 20.0 and GraphPad Prism 5.0 software (GraphPad Software, La Jolla, CA, USA).

RESULTS

1-Characterization of the FPBF in 30 non-SSc controls

The scale and 5 grades of FPBF are presented in **Figure 1A, B and C**. Demographical characteristics of the 30 controls are presented in **Table 1**. We firstly highlighted that the FPBF of the third finger (F_{III}) of the right hand properly reflected other FPBF: the correlation between FPBF

grading of F_{III} in the right hand and left hand was excellent in basal conditions (R=0.76, P<0.0001), after cold challenge (R=0.73, P<0.0001) and after warm bath (R=0.86, P<0.0001). The correlation between FPBF grading of F_{III} and F_{IV} of the same hand was also excellent in basal conditions (R=0.92, P<0.0001), after cold challenge (R=0.79, P<0.0001), and after warm bath (R=0.76, P<0.0001). The other associations were therefore explored using the FPBF of the F_{III} of the right hand, for practical considerations. The distribution of the different grades of FPBF from all evaluated fingers is shown in **Supplementary Figure 2A,** and for the F_{III} of the right hand in **Supplementary Figure 2B.**

In dynamic conditions: worsening of the grade of FPBF (losing one or more than one grade of FPBF) was significantly associated with cold challenge (OR=16.79 (2.00-140.90), p=0.001). By contrast, the warm hand bath was protective from a worsening of the FPBF (OR=0.06 (0.007-0.500), p=0.001). Similarly, warm hand bath induced an improvement of FPBF (changing from one grade to a higher grade) (OR=3.82 (1.15-12.71), p=0.024) and cold challenge was inversely associated with improvement of FPBF (OR=0.26 (0.79-0.87), p=0.024). Regarding FPBF distribution, a decreasing prevalence of grade 0, 1 and 2 was observed after warm bath with an increasing prevalence of grade 4 (**Supplementary Figure 2A and B**).

Regarding reproducibility, the inter-observer Kappa coefficient was almost perfect (K=0.82; AL visual reading compared to GC visual reading) and intra-observer Kappa coefficients were substantial (0.61 (GC) and 0.71 (AL)).

2-Association and FPBF and vasodilation status based on resistance index.

In dynamic conditions, cold challenge significantly increased RI (from 0.90 (IQR=0.10) in basal condition to 0.96 (IQR=0.08) in cold condition, p<0.001). Warm bath significantly decreased RI compared to basal RI (0.81 (IQR=0.15) and 0.90 (IQR=0.10) in warm and basal conditions respectively, p<0.001) and to RI after cold challenge (0.81 (IQR=0.15) and 0.96 (IQR=0.08) in warm and cold conditions respectively, p<0.001). These results demonstrated that radial RI properly reflected vasodilation status (**Supplementary Figure 1A and B**).

RI and the grade of FPBF were negatively correlated, showing that lower RI values, reflecting a vasodilated status, were associated with higher grades of FPBF, in basal conditions (R=-0.50, p<0.01) (**Figure 2A**), after cold bath (R=-0.43, p<0.05) (**Figure 2B**), and after warm bath (R=-0.61, p<0.001) (**Figure 2C**).

Accepted Article

3-Association of PFBF and severity of SSc-related vascular manifestations in 86 patients with SSc

Clinical characteristics of SSc patients are presented in **Table 2**. In comparison with non-SSc controls, the proportion of SSc patients with a FPBF grade 0 was higher (3.3% vs 22.1%, $p<0.05$). The proportion of SSc patients with a FPBF grade 0 was higher in patients with DUs, unilateral and/or bilateral UAO, use of vasodilators (**Figure 3A, B, C, D**). On the contrary, the proportion of patients with a FPBF grade 4 was lower in patients with DUs (**Figure 3A**). A pathological threshold of less than 2 (grade 0 or 1) was significantly associated with DU (OR=6.67, IC95% (2.31-19.21), $p<0.0001$).

DISCUSSION

This study explored the relevance of a visual semi-quantitative classification of FPBF based on the depth of doppler signal on a longitudinal view of the distal phalanx of the third right finger. Our results highlighted that FPBF assessment according to this grading strategy correlated with vasodilation status assessed by RI of the radial artery. The grade with the lowest perfusion flow (grade 0) was more frequent in SSc patients than in non-SSc controls, and was associated with DU and severity markers of macrovascular involvement such as UAO in SSc patients, whereas the grade with the highest perfusion flow was significantly associated with less DU (current or past). When applying the OMERACT filter to this classification of FPBF (25), we demonstrated that this grading strategy of FPBF based on visual reading had a substantial inter and intra-observer reproducibility. Using this method, vascular evaluation was conducted in 10 minutes by a trained rheumatologist, showing good feasibility. The dynamic approach based on the exposure to various temperatures in controls, demonstrated that this classification had a good sensitivity to change in this control population. The association of higher grade with exposure to high temperatures and lower grade with the cold challenge in controls suggested a relevant construct validity. The association with DU and the correlation with RI, *i.e.* vasodilation status, also strengthened its construct validity and truth in this control population. The grade 0 showed its ability to discriminate controls and SSc.

To date, only a few studies have proposed semi-quantitative classification of the FPBF in SSc (9,10). Schioppo and colleagues have recently suggested a grading strategy of FPBF based on the surface of hyperemia/Doppler positivity, including 4 grades (9). The first grade was similar to the grade 0 proposed in our classification; the other grades were derived from the semi-quantitative evaluation of hyperemia of synovitis and not depending on anatomical considerations of digital vascularization. Our classification is based on the hypothesis that the first vessels to be damaged in

Accepted Article

SSc would be the smallest digital vessels, *i.e.* the sub-epidermal network, with progressive obliteration of larger vessels, *i.e.* perforating artery and the proper digital pulp artery, when vascular involvement would become more severe (26,27). These anatomic considerations may explain that ischemic DU are classically localized on fingertips in SSc (4,28). The anatomic rationale of the FPBF classification proposed in our study also supports its face validity. In their study, Schioppo and colleagues did not find differences between SSc patients with and without DU (9). This might be explained either by a lack of statistical power, or, by the rationale of their grading of FPBF. Nonetheless, the predictive value of both classifications for the occurrence of new DU is still to be determined (29,30).

The limitations of our study include its cross-sectional design. Due to this design, we cannot rule out that the lower prevalence of DU in patients with grade 4, could be related to the impact of previous substance loss and DU-associated scars with subsequent destruction of the sub-epidermal network in other grades than grade 4. Nonetheless this could not explain the association between grade 0 and DU, as DU and associated scars almost never reach the proper digital pulp artery. The significant proportion of SSc patients with vasodilators in our study is another limitation. Nonetheless, this is inherent to a representative population of patients with SSc, as excluding patients with vasodilators would lead to a selection bias, since the patients without vasodilators would have a digital vasculopathy with less complication, and especially, a lower prevalence of recurrent/chronic DU (31). The impact of vasodilators did not limit the association of lower FPBF with severity markers of the vasculopathy in our work, as the proportion of patients with a grade 0 was higher in patients with vasodilators than in patients without. Before and after studies using vasodilators such as bosentan, sildenafil or prostacyclin analogs are still warranted to further explore the sensitivity to change of this PDUS classification of the FPBF in SSc patients (9,32–35).

We did not perform dynamic evaluations in patients with SSc, including exposure to cold and hot water, which is another limitation. This could have been informative as by contrast with non-SSc controls, SSc patients may fail to improve their FPBF after warm hand bath (36). This result would strengthen the hypothesis of destruction or obliteration of the sub-epidermal network and/or perforating branches in SSc (37). Nonetheless, this rises ethical issues especially concerning exposure to cold that could be experienced as painful by SSc patients and may trigger Raynaud's phenomenon attacks. For these reasons, we did not perform such experiments in patients with SSc in this observational study. We have not studied the association between FPBF and recent evaluation protocols proposed for the assessment of microangiopathy by video-capillaroscopy (38). We only evaluated Cutolo's pattern based on dermoscopic evaluation. We did not evaluate the correlation between the obliteration of proper palmar digital arteries and FPBF (27). Nonetheless, the objective

Accepted Article

of our study was to propose a practical protocol, easy to be performed by rheumatologists in real-life in addition to hand synovial assessment, as Power Doppler US is now a widely non-invasive available tool (12,15,23,39,40).

Our study only provides the first steps for the assessment of PDUS evaluation of FPBF. Further studies are needed and should be put on the research agenda to fully validate the relevance of PDUS as an assessment tool in SSc (25). The feasibility of this classification and the reproducibility of our results should be assessed by other teams using independent SSc cohorts (12,30). The test-retest reliability of this grading strategy should also be explored (41). The best threshold of FPBF that would define a pathologic blood perfusion of the fingers should also be assessed in prospective studies with a validation cohort. Such studies could confirm the relevance of grade 2 as the best threshold. The relevance of this PDUS classification of FPBF to predict the onset of new DU should also be assessed in SSc (29). Ultrasound evaluation allows the exploration of other digital manifestations of SSc such as sub-cutaneous calcinosis (12). We did not explore such manifestations in our work. The correlation of FPBF with calcinosis detected by ultrasound during the same examination should also be explored in future studies. A comparison of our classification with a grading of FPBF based on the surface of hyperemia/Doppler positivity should also be performed (9,10). The direct comparison of PDUS evaluation with other tools that reflect SSc-associated vasculopathy such as laser Doppler imaging technics or thermography may also deserve dedicated studies in the future (42).

The impact of therapeutics on our classification of FPBF still needs to be precisely determined in prospective studies, to explore if an improvement of FPBF by a vasodilator treatment is associated with a decrease in the occurrence of new SSc-associated digital manifestations such as DU (4). In the end, the objective could be the progressive combination of vasodilators to restore a significant FPBF, with the final goal of limiting new digital complications in a treat-to-target approach (43).

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. *The Lancet* 2017;390:1685–1699.

2. Lescoat A, Varga J, Matucci-Cerinic M, Khanna D. New promising drugs for the treatment of systemic sclerosis: Pathogenic considerations, enhanced classifications, and personalized medicine. *Expert Opin Investig Drugs* 2021.

3. Khanna D, Denton CP, Merkel PA, Krieg T, Le Brun F-O, Marr A, et al. Effect of Macitentan on the Development of New Ischemic Digital Ulcers in Patients With Systemic Sclerosis: DUAL-1 and DUAL-2 Randomized Clinical Trials. *JAMA* 2016;315:1975–1988.

4. Hughes M, Allanore Y, Chung L, Pauling JD, Denton CP, Matucci-Cerinic M. Raynaud

Accepted Article

phenomenon and digital ulcers in systemic sclerosis. *Nat Rev Rheumatol* 2020;16:208–221.
5. Pauling JD, Frech TM, Hughes M, Gordon JK, Domsic RT, Anderson ME, et al. Patient-reported outcome instruments for assessing Raynaud's phenomenon in systemic sclerosis: A SCTC Vascular Working Group Report. *J Scleroderma Relat Disord* 2018;3:249–252.
6. Murphy SL, Lescoat A, Alore M, Hughes M, Pauling JD, Sabbagh M, et al. How do patients define Raynaud's phenomenon? Differences between primary and secondary disease. *Clin Rheumatol* 2021;40:1611–1616.
7. Mouthon L, Poiraudeau S, Vernon M, Papadakis K, Perchenet L, Khanna D. Psychometric validation of the Hand Disability in Systemic Sclerosis-Digital Ulcers (HDISS-DU®) patient-reported outcome instrument. *Arthritis Res Ther* 2020;22:3.
8. Mouthon L, Carpentier PH, Lok C, Clerson P, Gressin V, Hachulla E, et al. Controlling the digital ulcerative disease in systemic sclerosis is associated with improved hand function. *Semin Arthritis Rheum* 2017;46:759–766.
9. Schioppo T, Orenti A, Boracchi P, De Lucia O, Murgo A, Ingegnoli F. Acute and chronic effects of two different intravenous iloprost regimens in systemic sclerosis: a pragmatic non-randomized trial. *Rheumatology (Oxford)* 2018;57:1408–1416.
10. Schioppo T, Orenti A, Boracchi P, De Lucia O, Murgo A, Ingegnoli F. Evidence of macro- and micro-angiopathy in scleroderma: An integrated approach combining 22-MHz power Doppler ultrasonography and video-capillaroscopy. *Microvasc Res* 2019;122:125–130.
11. Lescoat A, Coiffier G, Carlan M de, Droitcourt C, Ballerie A, Cazalets C, et al. Combination of Capillaroscopic and Ultrasonographic Evaluations in Systemic Sclerosis: Results of a Cross-Sectional Study. *Arthritis Care Res (Hoboken)* 2018;70:938–943.
12. Fairchild R, Chung M, Sharpless L, Li S, Chung L. Ultrasound Detection of Calcinosis and Association with Ulnar Artery Occlusion in Patients with Systemic Sclerosis. *Arthritis Care Res (Hoboken)* 2020.
13. Frerix M, Stegbauer J, Dragun D, Kreuter A, Weiner SM. Ulnar artery occlusion is predictive of digital ulcers in SSc: a duplex sonography study. *Rheumatology (Oxford)* 2012;51:735–742.
14. Lescoat A, Yelnik CM, Coiffier G, Wargny M, Lamotte C, Cazalets C, et al. Ulnar Artery Occlusion and Severity Markers of Vasculopathy in Systemic Sclerosis: A Multicenter Cross-Sectional Study. *Arthritis & Rheumatology (Hoboken, NJ)* 2019;71:983–990.
15. Fairchild R, Horomanski A, Sharpless L, Chung M, Li S, Hong J, et al. Ultrasound evaluation of the hands and wrists in patients with systemic sclerosis: Osteophytosis is a major contributor to tender joints. *Semin Arthritis Rheum* 2021;51:735–740.

Accepted Article

16. Caimmi C, De Marchi S, Bosello SL, Giuggioli D, Caramaschi P, Di Giorgio A, et al. Ultrasonography involvement of carotid, upper and lower limb arteries in a large cohort of systemic sclerosis patients. *Int J Rheum Dis* 2020;23:681–692.
17. Lescoat A, Coiffier G, Rouil A, Droitcourt C, Cazalets C, Carlan M de, et al. Vascular Evaluation of the Hand by Power Doppler Ultrasonography and New Predictive Markers of Ischemic Digital Ulcers in Systemic Sclerosis: Results of a Prospective Pilot Study. *Arthritis Care Res (Hoboken)* 2017;69:543–551.
18. Pauling JD, Hughes M, Pope JE. Raynaud's phenomenon—an update on diagnosis, classification and management. *Clin Rheumatol* 2019;38:3317–3330.
19. Hauck RM, Camp L, Ehrlich HP, Saggers GC, Banducci DR, Graham WP. Pulp nonfiction: microscopic anatomy of the digital pulp space. *Plast Reconstr Surg* 2004;113:536–539.
20. Hoogen F van den, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative: ACR/EULAR Classification Criteria for SSc. *Arthritis & Rheumatism* 2013;65:2737–2747.
21. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202–205.
22. Möller I, Janta I, Backhaus M, Ohrndorf S, Bong DA, Martinoli C, et al. The 2017 EULAR standardised procedures for ultrasound imaging in rheumatology. *Ann Rheum Dis* 2017;76:1974–1979.
23. Lescoat A, Ballerie A, Belhomme N, Cazalets C, Carlan M de, Droitcourt C, et al. Synovial involvement assessed by power Doppler ultra-sonography in systemic sclerosis: results of a cross-sectional study. *Rheumatology (Oxford)* 2018;57:2012–2021.
24. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276–282.
25. Boers M, Beaton DE, Shea BJ, Maxwell LJ, Bartlett SJ, Bingham CO, et al. OMERACT Filter 2.1: Elaboration of the Conceptual Framework for Outcome Measurement in Health Intervention Studies. *J Rheumatol* 2019;46:1021–1027.
26. Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. *Arthritis Rheum* 2013;65:1953–1962.
27. Lüders S, Friedrich S, Ohrndorf S, Glimm A-M, Burmester G-R, Riemekasten G, et al. Detection of severe digital vasculopathy in systemic sclerosis by colour Doppler sonography is associated with digital ulcers. *Rheumatology (Oxford)* 2017;56:1865–1873.
28. Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist.

Accepted Article

Arthritis Rheum 2004;50:3985–3993.
29. Friedrich S, Lüders S, Glimm AM, Werner SG, Schmittat G, Burmester GR, et al. Association between baseline clinical and imaging findings and the development of digital ulcers in patients with systemic sclerosis. *Arthritis Res Ther* 2019;21:96.
30. Friedrich S, Lüders S, Klotsche J, Burmester GR, Riemekasten G, Ohrndorf S. The first composite score predicting Digital Ulcers in systemic sclerosis patients using Clinical data, Imaging and Patient history-CIP-DUS. *Arthritis Res Ther* 2020;22:144.
31. Cutolo M, Herrick AL, Distler O, Becker MO, Beltran E, Carpentier P, et al. Nailfold Videocapillaroscopic Features and Other Clinical Risk Factors for Digital Ulcers in Systemic Sclerosis: A Multicenter, Prospective Cohort Study. *Arthritis Rheumatol* 2016;68:2527–2539.
32. Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum* 2004;50:3985–3993.
33. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2011;70:32–38.
34. Hachulla E, Hatron P-Y, Carpentier P, Agard C, Chatelus E, Jego P, et al. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. *Ann Rheum Dis* 2016;75:1009–1015.
35. Wigley FM, Wise RA, Seibold JR, McCloskey DA, Kujala G, Medsger TA, et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann Intern Med* 1994;120:199–206.
36. Hummers LK, Dugowson CE, Dechow FJ, Wise RA, Gregory J, Michalek J, et al. A multi-centre, blinded, randomised, placebo-controlled, laboratory-based study of MQX-503, a novel topical gel formulation of nitroglycerine, in patients with Raynaud phenomenon. *Ann Rheum Dis* 2013;72:1962–1967.
37. Kavian N, Batteux F. Macro- and microvascular disease in systemic sclerosis. *Vascul Pharmacol* 2015;71:16–23.
38. Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP, et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. *Autoimmunity Reviews* 2020;19:102458.
39. Santiago T, Santiago M, Ruaro B, Salvador MJ, Cutolo M, Silva J a. P da. Ultrasonography for the Assessment of Skin in Systemic Sclerosis: A Systematic Review. *Arthritis Care Res (Hoboken)*

Accepted Article

2019;71:563–574.
40. Lescoat A, Jégo P, Coiffier G, Caimmi C, Hachulla É. Imaging in Systemic Sclerosis: Make "US" Great Again? Comment on the Article by Santiago et al. *Arthritis Care Res (Hoboken)* 2019;71:694–695.
41. Omarjee L, Metairie A, Tueguem Moyo T, Pabic ELE, Jego P, Lescoat A, et al. Performance of finger systolic blood pressure measurement to detect digital occlusive arterial disease in systemic sclerosis. *Rheumatology (Oxford)* 2021:keab497.
42. Wilkinson JD, Leggett SA, Marjanovic EJ, Moore TL, Allen J, Anderson ME, et al. A Multicenter Study of the Validity and Reliability of Responses to Hand Cold Challenge as Measured by Laser Speckle Contrast Imaging and Thermography: Outcome Measures for Systemic Sclerosis-Related Raynaud's Phenomenon. *Arthritis & Rheumatology (Hoboken, NJ)* 2018;70:903–911.
43. Hughes M, Khanna D, Pauling JD. Drug initiation and escalation strategies of vasodilator therapies for Raynaud's phenomenon: can we treat to target? *Rheumatology (Oxford)* 2020;59:464–466.

Accepted Article

Accepted Article

ULTRASOUND CLASSIFICATION OF FINGER PULP BLOOD FLOW IN PATIENTS WITH SYSTEMIC SCLEROSIS: A PILOT STUDY

Alain Lescoat[1,2] MD PhD, François Robin[3,4] MD, Nicolas Belhomme[1,2] MD, Alice Ballerie[1,2] MD, Marine de Saint Riquier[3] MD, Martine Sebillot[1] MD, Jean-David Albert[3,4] MD, Thomas Le Gallou[1] MD, Aleth Perdriger[3] MD PhD, Patrick Jégo[1,2] MD PhD, Guillaume Coiffier[1,5*] MD, Claire Cazalets[1*] MD

1- *Department of Internal Medicine and Clinical Immunology, CHU Rennes, Univ Rennes, France*
2- *Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) – UMR_S 1085, F-35000 Rennes, France*
3- *Department of Rheumatology, CHU Rennes, Univ Rennes, France*
4- *INSERM, Univ Rennes, INRA, CHU Rennes, Institut NUMECAN (Nutrition Metabolisms and Cancer), F-35033 Rennes, France.*
5- *Department of Rheumatology, CH Dinan, France*

**Equal contribution*

3 Figures and 2 Tables

Accepted Article

Table 1: Clinical characteristics of the 30 controls

Characteristics	N (%) or Median (iQr/SD)
Demographic	
Age (years)	34.5 (11.3)
Men	9 (30.0)
Power doppler	
Basal conditions	
FPBF rFIII Grade 0	1 (3.3)
FPBF Grade 1	2 (6.7)
FPBF Grade 2	5 (16.7)
FPBF Grade 3	15 (50.0)
FPBF Grade 4	7 (23.3)
RI (mean of both hands) expressed as median (iQr)	0.91 (0.11)
UAO	2 (6.7)
Cold bath	
FPBF rFIII Grade 0	1 (3.3)
FPBF Grade 1	5 (16.7)
FPBF Grade 2	5 (16.7)
FPBF Grade 3	15 (50.0)
FPBF Grade 4	4 (13.3)
RI (mean of both hands) expressed as median (iQr)	0.96 (0.09)
Warm bath	
FPBF rFIII Grade 0	0 (0)
FPBF Grade 1	1 (3.3)
FPBF Grade 2	3 (10.0)
FPBF Grade 3	12 (40.0)
FPBF Grade 4	14 (46.7)
RI (mean of both hands) expressed as median (iQr)	0.81(0.14)

FPBF=Finger Pulp Blood Flow, *rFIII*= Third finger of the right hand, *RI*=Resistance Index ; *UAO*=Ulnar Artery Occlusion *; iQr*=Inter Quartile Range.

Accepted Article

Table 2: Clinical characteristics of the 86 SSc patients

Characteristics	N (%) or Mean (SD)
Demographic	
Age (years)	58.5 (11.26)
Men	18 (20.9)
Clinical characteristics	
Disease duration since RP symptom (years)	12.2 (11.66)
Disease duration since first non-RP symptom (years)	7.4 (8.1)
Diffuse cutaneous SSc	28 (32.6)
Modified Rodnan skin score > 8	23 (26.7)
Presence of skin telangiectasia	69 (80.2)
Cutolo's Late capillaroscopic pattern (n=63 data available)	25 (39.7)
DU ever	40 (46.5)
Pitting scars	38 (44.2)
ILD on CT scan	35 (40.7)
PAH on RHC	5 (5.8)
Immunological findings	
ACA	41 (47.7)
ATA/Scl70	23 (26.7)
RNA pol III	6 (7.0)
Other or negative	17 (19.8)
Therapeutics	
Calcium Channel Blockers	48 (55.8)
Bosentan	15 (17.4)
Sildenafil or tadalafil	6 (7.0)
IV Iloprost (history)	25 (29.1)
Immunosuppressive drugs	21 (24.4)
Power doppler	
Basal conditions	
FPBF rFIII Grade 0	19 (22.1)

Accepted Article

FPBF Grade 1	7 (8.1)
FPBF Grade 2	15 (17.4)
FPBF Grade 3	27 (31.4)
FPBF Grade 4	18 (20.9)
UAO	30 (34.9)

Accepted Article

Arthritis Care and Research
Original Article

Accepted Article

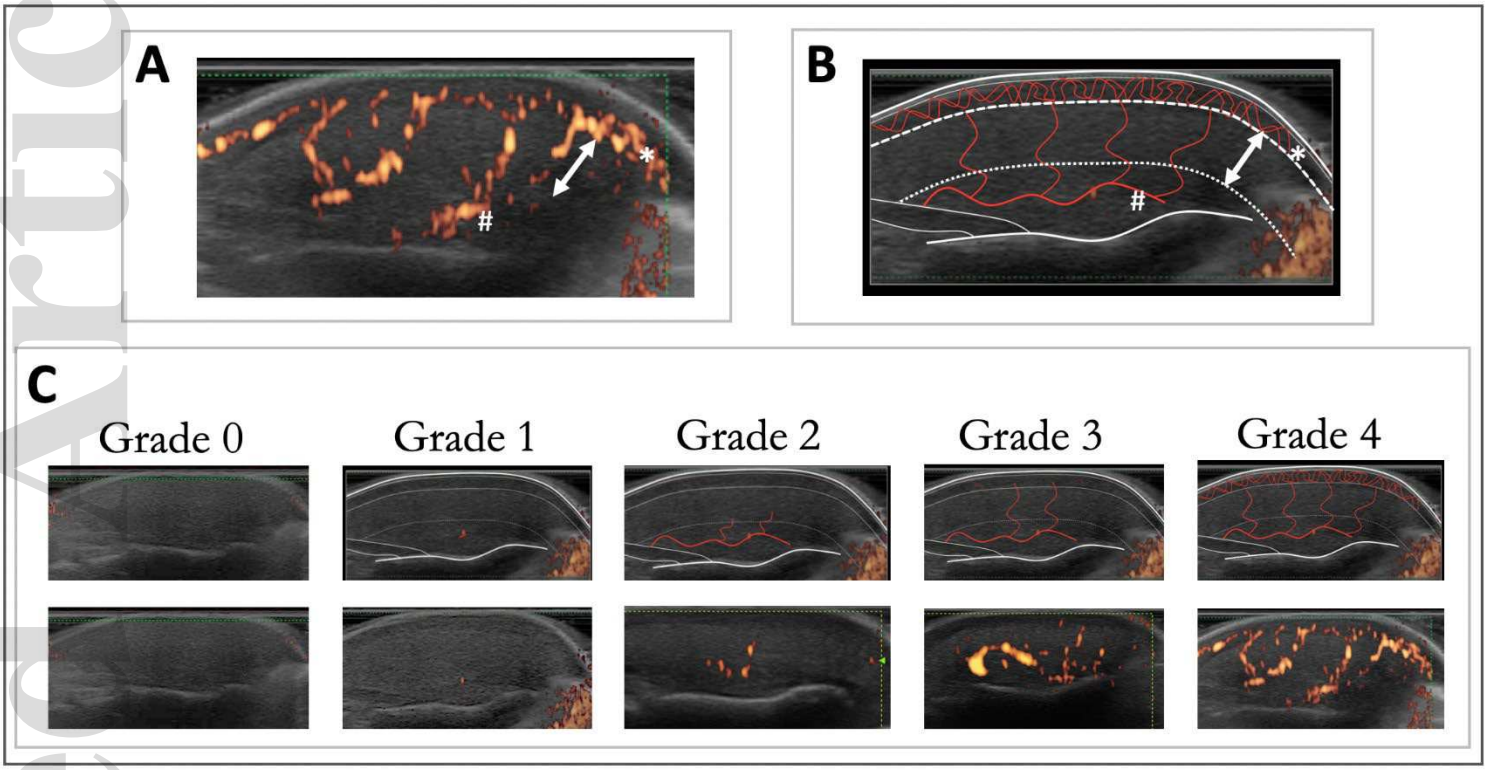


Figure 1: Classification of Finger Pulp Blood Flow (FPBF) according to Cazalets' classification.
A. and B. Anatomic considerations on the finger pulp: proper digital pulp artery (#), dermal and hypodermal perforating branches (double arrow), sub-epidermal anastomotic vascular network (*)
C. The five grades of Finger Pulp Blood Flow based on the depth of doppler positivity on a longitudinal view of the finger pulp.

Accepted Article

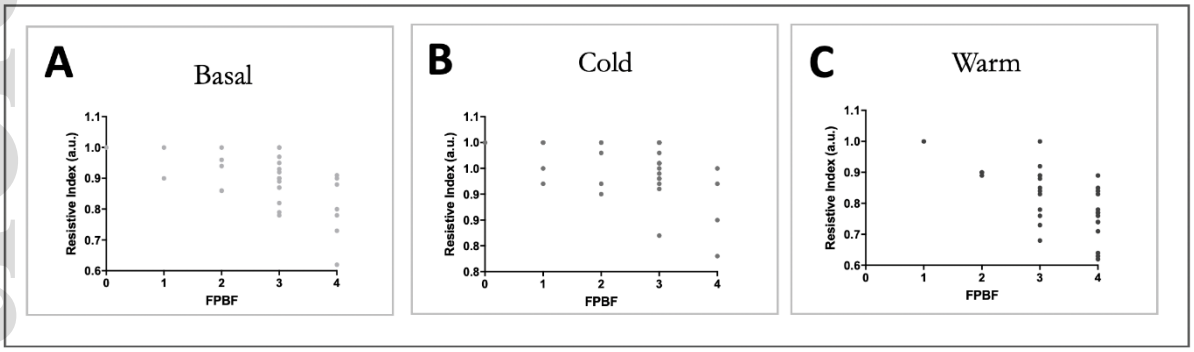


Figure 2: Correlation between Resistive Index of the radial artery and grade of FPBF
A. Correlation between RI and FPBF in basal conditions (spearman R=-0.50, p<0.01)
B. After exposure to cold (spearman R=-0.43, p<0.05)
C. After exposure to heat (spearman R=-0.61, p<0.001)

Accepted Article

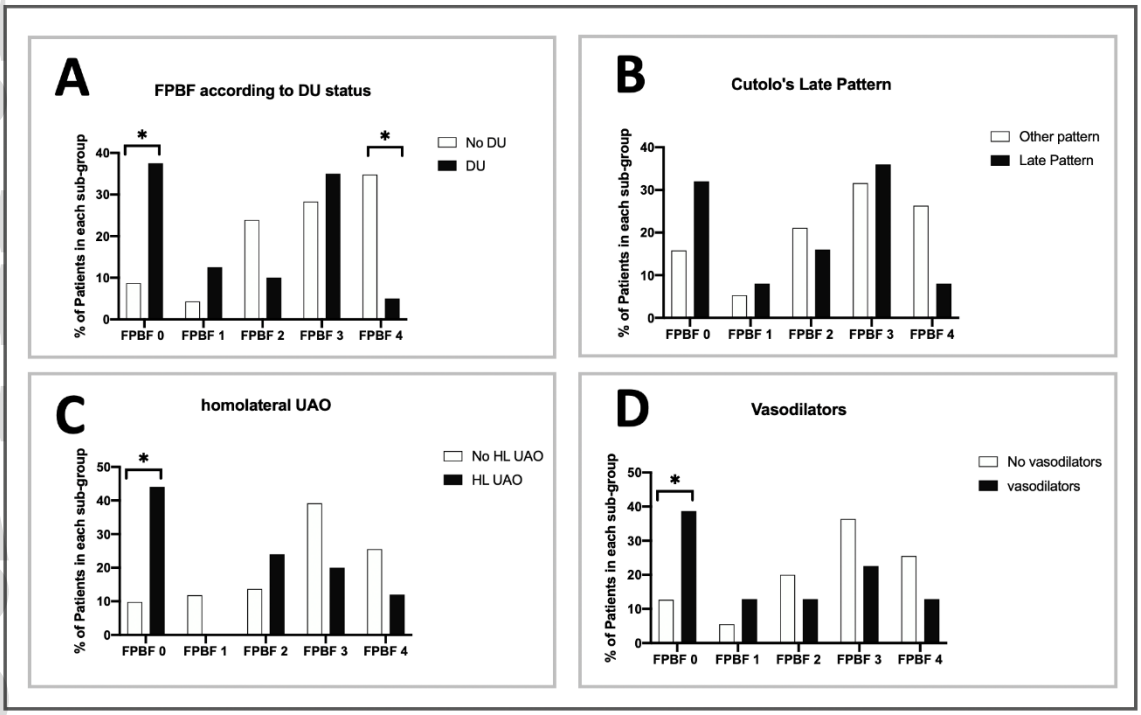


Figure 3: Distribution of the FPBF according to SSc associated clinical characteristics
A. Digital Ulcers (currently or previously); **B.** capillaroscopic pattern;
C. homolateral UAO; **D.** Vasodilator therapies (current or previously) ;
*p<0.05 (Fischer exact-test with Bonferroni correction)