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CLINICAL RESEARCH

Prediction of new onset of resting pulmonary arterial hypertension in systemic sclerosis

Facteurs prédictifs d'apparition d'hypertension artérielle pulmonaire chez les patients atteints de sclérodermie systémique

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KEYWORDS
Scleroderma;
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Pulmonary arterial hypertension;
Nailfold videocapillaroscopy

Summary
Background. — Early detection of pulmonary arterial hypertension (PH) is crucial in systemic scleroderma. However, predictors of new onset of resting PH during follow-up (FUPH) have been poorly explored.
Aim. — To determine whether nailfold videocapillaroscopy (NVC) grade and exercise echocardiographic variables are predictors of FUPH.
Methods. — We prospectively enrolled 40 patients with systemic sclerosis (age 54 ± 13 years; 68% women). All patients underwent graded semisupine exercise echocardiography and NVC. Baseline resting PH and FUPH were defined as systolic pulmonary arterial pressure (sPAP) > 35 mmHg, and exercise-induced PH (EIPH) as exercise sPAP > 50 mmHg.
Results. — Seventeen patients developed EIPH (43%). During follow-up (FU) (25 ± 15 months), 11 patients without baseline PH developed FUPH (28%), all from the EIPH group. Patients with FUPH

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; EIPH, exercise-induced pulmonary arterial hypertension; FUPH, new onset of resting pulmonary arterial hypertension during follow-up; HR, hazard ratio; LV, left ventricular; NVC, nailfold videocapillaroscopy; OR, odds ratio; PH, pulmonary arterial hypertension; sPAP, systolic pulmonary arterial pressure.

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were significantly older (60 ± 14 vs 50 ± 12 years; $P = 0.04$), had higher resting and exercise sPAP (30 ± 4 vs 22 ± 5 and 60 ± 12 vs 40 ± 11 mmHg, respectively; $P < 0.0001$) and a higher exercise E/e' ratio (9.4 ± 0.7 vs 5.8 ± 0.4; $P = 0.0003$) and presented more frequently NVC grade > 2 (90% vs 35%; $P = 0.0009$). After adjustment for age, resting sPAP, exercise sPAP and NVC grade > 2 were associated with maximal resting sPAP during follow-up and FUPH ($P < 0.05$). Patients with both EIPH and NVC grade > 2 had a very high incidence of FUPH (82%), and both variables remained strongly associated with FUPH after adjustment for age (hazard ratio 11.6, 95% confidence interval 2.4—55.3; $P = 0.002$).

Conclusion. — Exercise echocardiography and NVC can identify a subgroup of patients with systemic sclerosis who are at risk of developing FUPH.

MOTS CLÉS
Sclérodermie ;
Échocardiographie d'effort ;
Hypertension artérielle pulmonaire ;
Capillaroscopie

Résumé

Contexte. — Les facteurs prédictifs d'apparition d'HTAP pendant le suivi (HTAPsuivi), dans la sclérodermie systémique, demeurent mal connus.

Objectif. — Étudier si le stade de la capillaroscopie digitale (CD) et l'échocardiographie d'effort peuvent prédire l'HTAPSuivi.

Méthodes. — Quarante patients avec sclérodermie systémique ont été inclus (âge 54 ± 13 ans ; 68 % femme). Tous bénéficiaient d'une échocardiographie d'effort, et d'une CD. L'HTAP de repos était définie par une pression artérielle pulmonaire systolique (PAPs) > 35 mmHg, l'HTAP d'effort (HTAPeffort) par une PAPs d'effort > 50 mmHg.

Résultats. — Dix-sept patients (43 %) développaient une HTAPeffort. Pendant le suivi (25 ± 15 mois), 11 patients sans d'HTAP à l'inclusion, développaient une HTAPsuivi (28 %), tous avaient une HTAPEffort. Les patients avec une HTAPsuivi étaient plus âgés (60 ± 14 vs 50 ± 12 ans ; $p = 0,04$) avaient une PAPs de repos et d'effort plus hautes (respectivement, 30 ± 4 vs 22 ± 5 and 60 ± 12 vs 40 ± 11 mmHg ; $p < 0,0001$), un E/e' d'effort plus élevé (9,4 ± 0,7 vs 5,8 ± 0,4 ; $p = 0,0003$) et présentaient plus fréquemment un stade CD > 2 (90 % vs 35 % ; $p = 0,0009$). Après ajustement à l'âge, les PAPs de repos et d'effort ainsi que le stade CD > 2 étaient associées à la PAPs maximale de repos pendant le suivi et à l'apparition d'HTPSuivi ($p < 0,05$). Les patients avec une HTAPEffort et un stade CD > 2 avaient une incidence d'HTPsuivi très élevée (82 %). Après ajustement à l'âge, l'association de ces paramètres étaient fortement associée à l'HTPsuivi (HR 11,6, IC 2,4—55,3 ; $p = 0,002$).

Conclusion. — Dans la sclérodermie systémique, l'échocardiographie d'effort et la CD sont utiles pour identifier un groupe de patients à risque de développer une HTAPSuivi.

Background

Systemic sclerosis is a rare and complex autoimmune disease characterized by widespread vascular lesions and fibrosis leading to multiple organ impairment for the most severe presentation of the disease [1]. Lung, pulmonary circulation and myocardium impairment can lead to the development of pulmonary arterial hypertension (PH) caused by precapillary and/or post-capillary mechanisms. Early detection and treatment of PH is crucial in systemic sclerosis, as it is a main cause of death and poor outcome [2]. In systemic sclerosis, nailfold videocapillaroscopy (NVC) is an interesting tool for identifying microvascular impairment. Although some studies have shown the association of NVC with severe organ involvement [3], it has not been shown to be linked to the new onset of resting PH during follow-up (FUPH). Exercise-induced PH (EIPH) has recently been suggested as a potential highly sensitive tool for the early identification of patients with systemic sclerosis who are at risk of developing resting PH [4,5]. However, probably due to lack of specificity, it seems that the incidence of EIPH may overestimate the percentage of FUPH [6]. Although an examination of the haemodynamics of pulmonary circulation is of value [6,7], exercise echocardiography was not included in the last European Society of Cardiology recommendations [8], because of the ongoing debate about its usefulness in daily-life practice.

The present study sought to evaluate the usefulness of exercise echocardiography, B-type natriuretic peptide (BNP) blood concentration and NVC in an integrated screening approach for patients at risk of FUPH in systemic sclerosis.

Methods

From January 2008 to November 2012 we prospectively studied 68 consecutive patients with a diagnosis of systemic

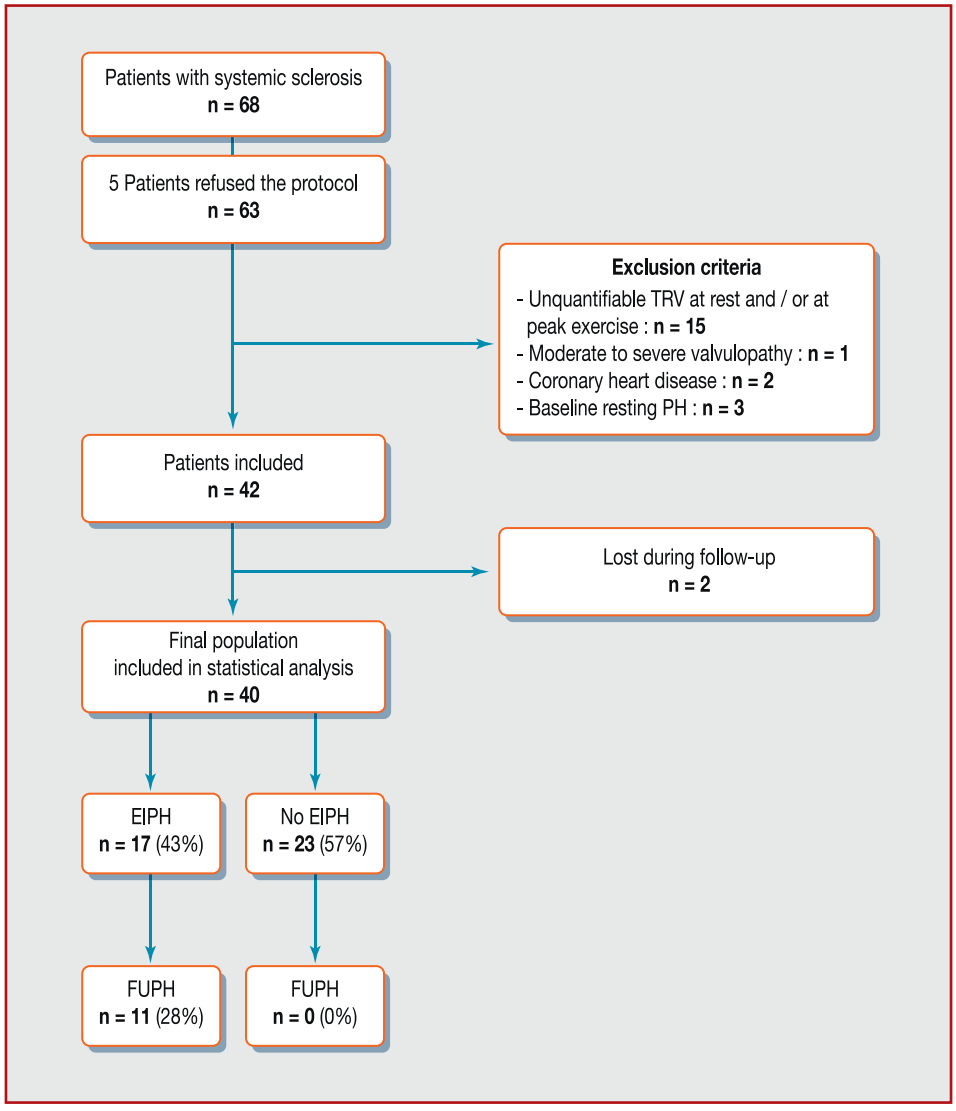

Figure 1. Study flow chart. EIPH: exercise-induced pulmonary hypertension; FUPH: onset of pulmonary arterial hypertension during follow-up; PH: pulmonary hypertension; TRV: tricuspid regurgitation velocity.

sclerosis followed in the rheumatology centre of CHU Sart-Tilman in Liège. Five patients refused to participate in the study. Exclusion criteria were inability to provide informed consent; previous ischaemic heart or valvular heart disease; inability to perform an exercise test; baseline resting PH; and unquantifiable systolic pulmonary arterial pressure (sPAP). Fifteen patients were excluded from the population ($n = 63$) because of unquantifiable sPAP (24% of the population), one for $\geq$ moderate mitral regurgitation, two for coronary artery disease and three for baseline resting PH (7% of patients with registrable tricuspid regurgitation). Finally, two patients were lost during follow-up, so the final analysis included 40 patients (Fig. 1). The relevant institutional review board approved the protocol, and all patients gave written informed consent.

Echocardiographic examination

All patients underwent comprehensive resting echocardiography, using a conventional method, with a Vivid 9 ultrasound system (General Electric Healthcare, Little Chalfont, UK), at baseline and during follow-up (twice a year), blinded for NVC results at baseline. Offline analysis was performed retrospectively using a customized software package (EchoPac). Left ventricular (LV) stroke volume was calculated as the difference between LV end-diastolic and end-systolic volumes assessed by the biapical Simpson's disc method, and LV ejection fraction was derived from the stroke volume/LV end-diastolic volume ratio. Cardiac output was obtained by multiplying LV, stroke volume and heart rate. Peak E wave and A wave velocities of the mitral inflow were measured with pulsed-wave Doppler. Tissue Doppler imaging was applied for the measurement of e' wave at the lateral mitral annulus aspect. Both measurements of E and A waves and tissue Doppler imaging at the mitral annulus level were performed during exercise, just before fusion of E and A waves. Right ventricular fractional area change, tricuspid annular plane systolic excursion and maximal systolic velocity of the tricuspid annulus (s') were assessed in all patients. The systolic pulmonary arterial pressure (sPAP) was derived

from the maximal velocity of the tricuspid regurgitant jet, according to the simplified Bernoulli equation, with the addition of right atrial pressure, estimated from the dimension and collapsibility of the inferior vena cava [9]. A peak value > 35 mmHg was considered to define resting PH [10] at baseline and FUPH. At peak exercise, sPAP was derived from the tricuspid regurgitant jet velocity, with the addition of 10 mmHg for the estimation of right atrial pressure [11]. EIPH was defined as sPAP > 50 mmHg [12]. mPAP was estimated using the Chemla formula: mPAP = 0.61 × sPAP + 2. The slope of the mPAP/LVCO relationship was estimated as the ratio between changes (peak − rest value) in mPAP and changes in LVCO [13,14]. All echocardiographic variables were acquired at peak exercise, except for mitral inflow velocities and tissue Doppler imaging at the mitral annulus.

A symptom-limited graded bicycle exercise test was performed in a semisupine position on a tilted table. After an initial workload of 25 W maintained for 2 minutes, the workload was gradually increased by 25 W every 2 minutes. A 12-lead electrocardiogram was monitored continuously, and blood pressure was measured at rest and at each level of exercise. All patients presented normal tests, defined as the absence of the occurrence of: angina; ≥2 mm ST-segment depression compared with baseline level; or complex ventricular arrhythmias.

NVC and lung function assessment

Using an optical probe videocapillaroscope, the nailfold of the second, third, fourth and fifth fingers was examined bilaterally in each patient as described previously [3]. NVC grades were qualitatively assessed as normal (grade 1: normal capillary morphology, regular distribution and no capillary loss), early (grade 2: few capillary microhaemorrhages and giant capillaries, no loss of capillaries and preserved distribution), active (grade 3: frequent capillary microhaemorrhages and giant capillaries, moderate loss of capillaries, mild disorganization of the microvascular architecture and absent or mild ramified capillaries) and late (grade 4: irregular enlargement of capillaries, few or absent giant capillaries and microhaemorrhages, severe loss of capillaries and large avascular areas, disorganization of capillary and ramified capillary).

All patients underwent standard pulmonary function tests, with assessment of total lung capacity, vital capacity, forced vital capacity, forced expiratory volume in 1 second, ratio of forced expiratory volume in 1 second to vital capacity and diffusing capacity of the lung for carbon monoxide.

BNP blood concentration assessment

BNP blood concentration was assessed at rest, just before echocardiography examination, in a subset of 30 patients. Venous blood samples were drawn before echocardiography, after 10 minutes of supine rest. Chilled ethylenediaminetetraacetic acid tubes were centrifuged immediately at 4000 rpm (4—8 °C) for 15 minutes.

Statistical analysis

Continuous variables are expressed as means ± standard deviations; categorical variables are presented as numbers and percentages. Data comparisons were performed according to the presence or absence of FUPH using Student's unpaired and paired *t* tests, the χ^2 test or Fisher's exact test, as appropriate. The relationships between maximal sPAP during follow-up and other continuous variables (i.e. demographic data, resting and exercise echocardiographic data) were evaluated by simple linear regression. Predictors of highest sPAP during follow-up were identified with the use of univariate and multivariable linear regressions. Univariate and multivariable logistic regression and Cox proportional-hazards models analyses were performed to define predictors of FUPH. In all multivariable analyses, because of the sample size and the limited number of outcome data, adjustments were performed with only two variables in order to limit statistical power reduction and to avoid type II error. The value of χ^2 for each variable defined its prognostic value. Sequential Cox models were performed to determine the incremental prognostic benefit of different variables over age. A statistically significant increase in the global log-likelihood χ^2 of the model defined incremental prognostic value. Probabilities of FUPH-free survival were obtained by Kaplan-Meier estimates, and then compared using a two-sided log-rank test. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed with SPSS software, version 16.0.

Results

Population characteristics

The mean age of the population was 54 ± 13 years; 68% were women. sPAP increased significantly during exercise (from 24 ± 6 to 46 ± 14 mmHg; $P < 0.0001$). Seventeen (43%) patients developed EIPH. After a mean follow-up of 25 ± 15 months (median 28 months), 11 patients (28%) had FUPH, all in the EIPH group. Patients with EIPH and FUPH were significantly older (62 ± 12 vs 48 ± 11 years and 60 ± 14 vs 50 ± 12 years, respectively; $P < 0.05$ in both cases). Female sex was more frequent in the EIPH group (90% vs 62%; $P = 0.03$), but not in the FUPH group (64% vs 69%; $P = 0.69$. There were no significant differences between the two groups regarding medication and lung function test variables (Table 1). There were no significant differences between the two groups in terms of Raynaud's phenomenon (82% vs 87%; $P = 1.00$ or the presence of Scl-70 antibodies (36% vs 31%; $P = 0.70$. Patients with FUPH had a higher BNP blood concentration (79 ± 86 vs 23 ± 21 pg/mL; $P = 0.01$).

NVC grades

NVC grade 1 was found in 8% of patients, grade 2 in 38%, grade 3 in 28% and grade 4 in 20% (eight patients). There was a significant relationship between the different NVC grades and the onset of PH during follow-up ($P = 0.01$) (Fig. 2). Patients with FUPH presented more frequently NVC grade 4 (45% vs 11%; $P = 0.03$) and less frequently NVC grade 2 (54% vs 9%; $P = 0.006$). There were no significant differences between the FUPH and no FUPH groups regarding NVC grade 1 (0 vs 12%; $P = 0.13$) and grade 3 (45 vs 23%; $P = 0.18$). There was a significantly higher proportion of NVC > grade 2 in the FUPH group (90% vs 35%; $P = 0.0009$).

Table 1 Demographic, clinical and exercise data.

Variables	Whole cohort ($n = 40$)	No FUPH ($n = 29$, 72%)	FUPH ($n = 11$, 28%)	P
Demographic, clinical and biological data				
Age (years)	54 ± 13	50 ± 12	60 ± 14	0.04
Female sex	27 (68)	20 (69)	7 (64)	0.69
Body mass index (kg/m^2)	24 ± 5	24 ± 5	25 ± 6	0.72
Heart rate (bpm)	74 ± 14	73 ± 13	74 ± 16	0.72
Systolic arterial pressure (mmHg)	128 ± 19	126 ± 19	134 ± 16	0.36
Diastolic arterial pressure (mmHg)	73 ± 9	73 ± 10	74 ± 7	0.90
Raynaud's phenomenon	34 (85)	25 (87)	9 (82)	1.00
Delay between diagnosis and TTE (months)	36 ± 36	37 ± 39	31 ± 28	0.62
NYHA class > II	3 (8)	3 (10)	0 (0)	0.26
Presence of Scl-70 antibodies	13 (33)	9 (31)	4 (36)	0.70
BNP (pg/mL)	41 ± 61	23 ± 21	79 ± 86	0.01
Risk factors				
Systemic hypertension	4 (10)	2 (7)	2 (11)	0.33
Hypercholesterolaemia	9 (23)	7 (25)	2 (18)	0.64
Smoker	10 (24)	9 (31)	1 (9)	0.08
Family history of CV disease	2 (5)	2 (7)	0 (0)	0.24
Pulmonary function				
Total lung capacity (% predicted)	93 ± 21	95 ± 21	82 ± 16	0.15
Vital capacity (% predicted)	104 ± 24	105 ± 26	96 ± 17	0.32
Force vital capacity (% predicted)	101 ± 25	102 ± 21	93 ± 17	0.30
FEV1 (% predicted)	95 ± 20	96 ± 20	87 ± 22	0.27
FEV1/vital capacity (% predicted)	99 ± 12	100 ± 12	96 ± 13	0.38
DLCO (% predicted)	65 ± 14	66 ± 15	60 ± 12	0.33
Medication				
ACE inhibitors	2 (5)	1 (4)	1 (10)	0.51
Beta-blockers	3 (8)	1 (4)	2 (9)	0.15
Diuretics	2 (5)	1 (4)	1 (10)	0.51
Calcium inhibitors	20 (50)	13 (52)	7 (70)	0.32
Corticoids	9 (23)	5 (20)	4 (40)	0.23
Immunosuppressors	6 (16)	4 (16)	2 (20)	0.77
Exercise data				
Workload (W)	75 ± 31	81 ± 30	65 ± 36	0.22
Duration of exercise (minutes)	4.9 ± 1.3	4.7 ± 1.3	5.1 ± 1.6	0.55
Heart rate (bpm)	119 ± 17	119 ± 16	122 ± 21	0.65
Systolic arterial pressure (mmHg)	168 ± 23	163 ± 23	176 ± 21	0.19
Diastolic arterial pressure (mmHg)	82 ± 12	81 ± 11	84 ± 13	0.55

Data are expressed as mean ± standard deviation or number (%). ACE: angiotensin-converting enzyme; BNP: B-type natriuretic peptide; bpm: beats per minute; CV: cardiovascular; DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 second; FUPH: onset of pulmonary hypertension during follow-up; NYHA: New York Heart Association; TTE: transthoracic echocardiography.

Resting and exercise echocardiography

Patients with FUPH had higher baseline sPAP (30 ± 4 vs 22 ± 5 mmHg; $P < 0.0001$, baseline mPAP (20 ± 2 vs 15 ± 3 mmHg; $P < 0.0001$), indexed left atrial area (10 ± 3 vs 8 ± 1 cm^2; $P = 0.01$), exercise sPAP (60 ± 12 vs 40 ± 11 mmHg; $P < 0.0001$; Fig. 3), exercise mPAP (38 ± 7 vs 26 ± 7 mmHg; $P < 0.0001$) and exercise-induced changes in sPAP (+25 ± 10 vs +14 ± 9 mmHg; $P = 0.001$) (Tables 2 and 3). Patients with EIPH had a higher exercise E/e' ratio (9.1 ± 1.2 vs 5.7 ± 1.4; $P = 0.0002$). During exercise (Table 3), LV ejection fraction (67 ± 5 vs 71 ± 5%; $P = 0.001$) and its rate of change (+4 ± 3 vs +8 ± 4%; $P = 0.008$) were lower in the FUPH group. Conversely, the E/e' ratio, resulting from lower e' wave velocity, was higher in the FUPH group (9.4 ± 0.7 vs 5.8 ± 0.4 [$P = 0.0003$] and 17 ± 0.1 vs 12 ± 0.2 cm/s [$P = 0.03$], respectively). The slope of the mPAP-LVCO relationship (6.7 ± 2.7 vs 3.4 ± 2.1 mmHg/L/min; $P = 0.003$) was higher in the FUPH group.

Finally, 40% of patients presented neither EIPH nor NVC grade > 2, 32% presented either EIPH or NVC grade > 2 and 18% had both EIPH and NVC grade > 2. There was a significant difference in the incidence of FUPH between patients with no EIPH and NVC grade < 2 and patients with EIPH or NVC grade > 2, and those who had both EIPH and NVC grade > 2 (0% vs 17% vs 82%, respectively; $P < 0.0001$).

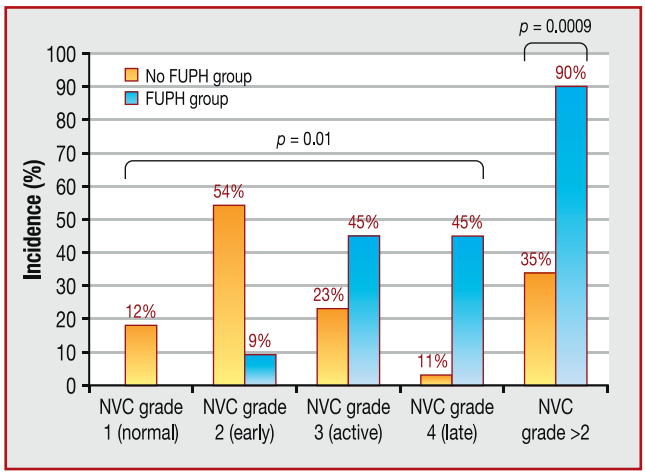

Figure 2. Comparison of the incidence of nailfold videocapillaroscopy (NVC) grades according to the two groups. FUPH: onset of pulmonary arterial hypertension during follow-up.

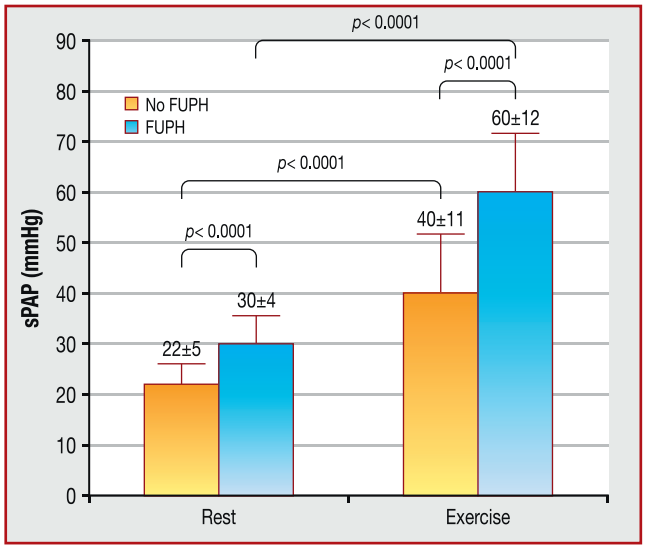

Figure 3. Comparison of resting and exercise systolic pulmonary arterial pressure (sPAP) according to the two groups. FUPH: onset of pulmonary arterial hypertension during follow-up.

Determinants of the maximal value of sPAP during follow-up

A significant correlation was found between maximal sPAP during follow-up and exercise left atrial pressure ($r^2 = 0.43$; $P < 0.004$), as well as resting indexed left atrial area ($r^2 = 0.43$; $P < 0.0001$), resting sPAP ($r^2 = 0.36$; $P < 0.0001$), exercise sPAP ($r^2 = 0.36$; $P < 0.0001$), the slope of the mPAP-LVCO relationship ($r^2 = 0.22$; $P = 0.01$) and exercise indexed right atrial area ($r^2 = 0.31$; $P = 0.002$). A correlation was found with age ($r^2 = 0.18$; $P = 0.009$) and exercise-induced changes in LV ejection fraction ($r^2 = 0.15$; $P = 0.01$).

After adjustment for age, resting sPAP and exercise sPAP remained independently associated with maximal resting sPAP during follow-up ($\beta = 0.9 \pm 0.3$ [$P = 0.02$] and $\beta = 0.4 \pm 0.1$ [$P = 0.02$], respectively), as did NVC grade > 2 ($\beta = 9.1 \pm 2.9$; $P = 0.004$).

In the subgroup of 30 patients with BNP blood concentration measurements available, BNP was related to the maximal value of sPAP during follow-up ($r^2 = 0.41$; $P < 0.001$) and remained associated after adjustment for age ($\beta = 0.1 \pm 0.03$; $P = 0.001$).

Determinants of FUPH

Logistic regression analyses

Age was associated with the onset of PH during follow-up (odds ratio [OR] 1.06; 95% confidence interval [CI] 1.01—1.13; $P = 0.047$), as were resting sPAP and exercise sPAP (OR 1.71, 95% CI 1.19—2.45 [$P = 0.003$] and OR 1.18, 95% CI 1.06—1.32 [$P = 0.003$], respectively). Similarly, NVC grade > 2 was related to FUPH (hazard ratio [HR] 18.9, 95% CI 2.1—172; $P = 0.009$).

After adjustment for age, resting sPAP and exercise sPAP remained associated with FUPH (odds ratio 1.68, 95% CI 1.17—2.4 [$P = 0.005$] and OR 1.17, 95% CI 1.05—1.32 [$P = 0.006$], respectively), as did NVC grade > 2 (OR 16.9, 95% CI 1.7—168; $P = 0.02$).

Beyond age ($\chi^2 = 4.5\%$), there was an incremental value for NVC grade > 2 ($\chi^2 = 14.1\%$; $P < 0.0001$), resting sPAP ($\chi^2 = 22.1\%$) and EIPH ($\chi^2 = 25.2\%$; $P < 0.0001$) to predict FUPH (Fig. 4).

In the subgroup of 30 patients with BNP concentration measurements available, BNP was not associated with FUPH (OR 1.04, 95% CI 0.99—1.08; $P = 0.054$).

Time-dependency statistical analyses

After a follow-up of 24 months, patients with NVC grade > 2 and EIPH had lower FUPH-free survival rates ($61.8 \pm 11.4\%$ vs 100% [$P < 0.05$] and $55.4 \pm 12.8\%$ vs 100% [$P < 0.05$], respectively). In addition, patients with no EIPH and NVC grade < 2 had a greater FUPH-free survival rate than patients with either EIPH or NVC grade > 2 and patients with both EIPH and NVC grade > 2 (100% vs $75.8 \pm 15.6\%$ vs $41.6 \pm 15.6\%$, respectively; $P = 0.0001$).

In Cox regression analyses, age was associated with FUPH (HR 1.06, 95% CI 1.02—1.11; $P = 0.007$), as were resting sPAP and exercise sPAP (HR 1.41, 95% CI 1.18—1.69 [$P = 0.0001$] and HR 1.16, 95% CI 1.08—1.25 [$P = 0.0001$], respectively). NVC grade > 2 was associated with the onset of PH during follow-up (HR 8.9, 95% CI 1.13—69.4; $P = 0.04$). Finally, the combination of EIPH and NVC grade > 2 was related to FUPH (HR 15.1, 95% CI 3.2—70.3; $P = 0.001$).

After adjustment for age, resting sPAP and exercise sPAP were associated with FUPH (HR 1.41, 95% CI 1.08—1.70 [$P = 0.0001$] and HR 1.2, 95% CI 1.08—1.25 [$P = 0.0001$], respectively), as was NVC grade > 2 (HR 9.1, 95% CI 1.1—74.8; $P = 0.04$). Finally, EIPH and NVC grade > 2 also remained associated with FUPH (HR 11.6, 95% CI 2.4—55.3; $P = 0.002$).

Beyond age ($\chi^2 = 7.7\%$), there was an incremental value for NVC grade > 2 ($\chi^2 = 11.8\%$; $P < 0.0001$), resting sPAP ($\chi^2 = 16.1\%$; $P < 0.0001$), EIPH ($\chi^2 = 21.3\%$; $P < 0.0001$) and the combination of EIPH and NVC grade > 2 ($\chi^2 = 23.8\%$; $P < 0.0001$) to predict FUPH (Fig. 4).

In the subset of 30 patients with BNP concentration measurements available, BNP was associated with FUPH (HR 1.02, 95% CI 1.01—1.03; $P = 0.004$), and this association

Table 2 Resting echocardiographic data.

Variables	Whole cohort ($n=40$)	No FUPH ($n=29$, 72%)	FUPH ($n=11$, 28%)	P
Resting LV echocardiographic data				
LV indexed end-diastolic volume (mL)	45 ± 11	47 ± 13	42 ± 7	0.30
LV indexed end-systolic volume (mL)	16 ± 5	17 ± 7	15 ± 3	0.48
LV indexed stroke volume (mL)	29 ± 6	30 ± 7	28 ± 5	0.40
Simpson's LVEF (%)	63 ± 4	64 ± 4	62 ± 5	0.41
Cardiac output (L/min)	3.7 ± 0.9	3.7 ± 0.2	3.5 ± 0.3	0.65
E (cm/s)	6.9 ± 1.3	6.9 ± 0.2	7.1 ± 0.5	0.75
E deceleration time (ms)	179 ± 37	179 ± 7	172 ± 13	0.75
A (cm/s)	6.7 ± 1.8	6.7 ± 0.3	7.2 ± 0.6	0.63
E/A ratio	1.1 ± 0.5	1.1 ± 0.1	1.2 ± 0.2	0.59
e' (cm/s)	1.1 ± 0.5	1.3 ± 0.1	1.1 ± 0.1	0.10
E/e' ratio	5.9 ± 1.7	5.6 ± 0.3	6.8 ± 0.6	0.08
Resting RV echocardiographic data				
RV/LV ratio	0.75 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.30
RV end-diastolic area (cm^2)	13.9 ± 3.7	14.1 ± 4.2	13.3 ± 2.4	0.53
RV end-systolic area (cm^2)	7.2 ± 2.3	7.5 ± 2.4	7.0 ± 2.1	0.59
RVFAC (%)	47.8 ± 8.8	47.3 ± 7.7	47.4 ± 10.2	0.98
TAPSE (mm)	23 ± 5	23 ± 4	24 ± 6	0.77
s' (cm/s)	12.3 ± 2.7	12.5 ± 2.6	12.6 ± 2	0.89
ICV max (cm/s)	12 ± 4	12 ± 4	13 ± 3	0.33
IVRT (ms)	46 ± 23	49 ± 22	41 ± 29	0.39
MPI	0.36 ± 0.14	0.35 ± 0.12	0.38 ± 0.19	0.63
Pulmonary acceleration time (ms)	138 ± 35	144 ± 35	119 ± 31	0.06
sPAP (mmHg)	24 ± 6	22 ± 5	30 ± 4	<0.0001
mPAP (mmHg)	16 ± 4	15 ± 3	20 ± 2	<0.0001
Resting atrial area				
LA indexed area (cm^2)	8 ± 2	8 ± 1	10 ± 3	0.01
RA indexed area (cm^2)	7 ± 3	7 ± 1	9 ± 4	0.03

Data are expressed as mean ± standard deviation. FUPH: onset of pulmonary hypertension during follow-up; ICV: isovolumic contraction velocity; IRVT: isovolumic relaxation time; LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; mPAP: mean pulmonary arterial pressure; MPI: myocardial performance index; RA: right atrial; RV: right ventricular; RVFAC: right ventricular fractional area change; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion.

remained significant after adjustment for age (HR 1.02, 95% CI 1.01—1.03; $P=0.01$).

Discussion

The present study shows that: the development of PH at follow-up is not a rare condition in patients with systemic sclerosis (28%); NVC grade > 2 is a powerful predictor of the onset of FUPH in patients with systemic sclerosis; and exercise sPAP can predict the evolution of resting sPAP during FU. Our data also suggest that an integrated approach based upon both comprehensive exercise echocardiography and NVC could be useful in identifying a subgroup of patients with systemic sclerosis at higher risk of developing PH.

NVC grade and onset of resting PH

NVC is an interesting tool in systemic sclerosis for investigating the underlying disease lesion. However, it has been poorly explored, and its potential role in predicting FUPH has, to the best of our knowledge, hardly been studied. A few studies have reported a correlation between worsening NVC grade and severe organ involvement. Smith et al. [3] showed the potential clinical significance of NVC in 66 patients with systemic sclerosis; the authors classified microvascular lesions within four different stages, depending on the presence and importance of giant capillaries, microhaemorrhages and loss of capillaries (i.e. from ''normal'' to ''late'' NVC grade). Patients were followed-up clinically at 18—24 months, and severe organ involvement of the nine organ systems was studied. The authors demonstrated a close relationship between worsening NVC grade and future severe peripheral vascular involvement, as well as future severe lung involvement. Similarly, we demonstrated a close relationship between NVC grade > 2 and FUPH, strengthening the potential clinical value of NVC in risk stratification of patients with systemic sclerosis. These results suggest that local microvascular status probably represents global microvascular impairment, and is linked to myocardial and pulmonary microvascular status, as suggested by resting and exercise echocardiography data

Table 3 Exercise echocardiographic data.

Variables	Whole cohort ($n=40$)	No FUPH ($n=29$, 72%)	FUPH ($n=11$, 28%)	P
Exercise LV echocardiographic data				
LV indexed end-diastolic volume (mL)	50 ± 11	51 ± 13	47 ± 6	0.36
LV indexed end-systolic volume (mL)	15 ± 5	15 ± 5	16 ± 3	0.79
LV indexed stroke volume (mL)	35 ± 8	36 ± 9	31 ± 3	0.15
Simpson's LVEF (%)	0 ± 5	71 ± 5	67 ± 5	0.001
Cardiac output (L/min)	7.2 ± 2.1	7.6 ± 0.4	6.2 ± 0.8	0.15
E (cm/s)	9.8 ± 1.9	9.6 ± 1.9	10.0 ± 2.2	0.21
E deceleration time (ms)	118 ± 37	114 ± 8	118 ± 19	0.86
A (cm/s)	9.4 ± 1.7	9.2 ± 0.3	10.1 ± 0.8	0.34
E/A ratio	1.1 ± 0.2	1.1 ± 0.1	1.0 ± 0.1	0.76
e' (cm/s)	1.6 ± 0.4	1.7 ± 0.1	1.2 ± 0.2	0.03
E/e' ratio	6.5 ± 1.4	5.8 ± 0.4	9.4 ± 0.7	0.0003
Exercise RV echocardiographic data				
RV end-diastolic area (cm^2)	12.1 ± 2.9	12.0 ± 3.0	12.5 ± 3.3	0.71
RV end-systolic area (cm^2)	5.7 ± 1.6	5.8 ± 1.8	5.5 ± 1.1	0.67
RVFAC (%)	52.6 ± 10	51.9 ± 9.6	54.2 ± 11.8	0.59
LV end-diastolic diameter, (mm)	39.6 ± 4.8	40.6 ± 4.9	36.6 ± 4.1	0.05
RV/LV ratio	71.0 ± 12	69.3 ± 12.2	79.4 ± 10.7	0.04
TAPSE (mm)	27.1 ± 5.4	26.5 ± 3.5	29.3 ± 8.4	0.15
s' (cm/s)	16.3 ± 3.7	16.9 ± 3.8	14.7 ± 3.3	0.18
ICV max (cm/s)	15.7 ± 4.8	15.5 ± 5.4	15.7 ± 2.4	0.95
IVRT (ms)	37.4 ± 15.7	35 ± 12	44 ± 26	0.32
sPAP (mmHg)	46 ± 14	40 ± 11	60 ± 12	<0.0001
mPAP (mmHg)	29 ± 8	26 ± 7	38 ± 7	<0.0001
Slope of mPAP[a] (mmHg/L/min)	4.2 ± 2.7	3.4 ± 2.1	6.7 ± 2.7	0.003
EIPH	17 (43)	6 (21)	11 (100)	<0.0001
Exercise atrial area				
LA indexed area (cm^2)	9 ± 3	8 ± 2	10 ± 5	0.09
RA indexed area (cm^2)	8 ± 3	7 ± 1	10 ± 5	0.03

Data are expressed as mean ± standard deviation or number (%). EIPH: exercise-induced pulmonary hypertension; FUPH: onset of pulmonary hypertension during follow-up; ICV: isovolumic contraction velocity; IRVT: isovolumic relaxation time; LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; mPAP: mean pulmonary arterial pressure; RA: right atrial; RV: right ventricular; RVFAC: right ventricular fractional area change; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion.

[a] Slope of mPAP indicates the ratio between changes in mPAP and changes in LVCO.

(i.e. higher exercise E/e' and lower exercise-induced change in these variables in the FUPH group).

Exercise echocardiography and evolution of sPAP

The accuracy of exercise echocardiography in detecting the development of PH during exercise in systemic sclerosis has been reported by several authors. Steen et al. [5] reported an EIPH incidence of 44% (defined by a post-exercise ≥ 20 mmHg increase in sPAP) in 54 patients. Using right heart catheterization, the authors confirmed the involvement of a precapillary mechanism in the vast majority of cases and, less frequently, a post-capillary aetiology. Of note, four patients had resting PH not detected by echocardiography, and only one patient had normal catheterization. The potential clinical significance of EIPH was demonstrated by Alkotob et al. [4] in 65 patients; they found a similar rate of EIPH (46%), with a slightly different definition of EIPH (exercise sPAP > 40 mmHg). Finally, they showed a relationship between EIPH and decreased exercise capacity, with a weak inverse relationship between exercise sPAP and maximal workload achieved ($r=-0.34$; $P=0.006$) or exercise duration ($r=-0.31$; $P=0.01$). Nevertheless, despite these findings, the potential role of EIPH and exercise echocardiography for the risk stratification of patients with PH was little highlighted in the last European recommendations [8]. In fact, only one recent study reported a significant relationship between exercise sPAP and FUPH in systemic sclerosis [15]. Using exercise echocardiography in a cohort of 170 patients with systemic sclerosis, Codullo et al. [15] found that patients who developed PH during follow-up (3.5 ± 0.2 years) had markedly significant higher exercise sPAP, exercise-induced change in sPAP and change in PAP indexed to change in cardiac output. In a multivariable analysis, the occurrence of FUPH (defined as mPAP ≥ 25 mmHg in right heart catheterization) was best predicted by exercise-induced changes in sPAP. Although the definitions of EIPH

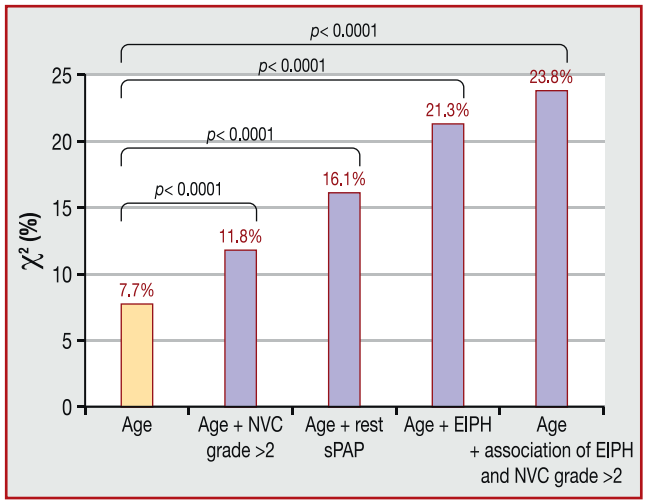

Figure 4. Incremental value over age of nailfold videocapillaroscopy (NVC) grade, resting systolic pulmonary arterial pressure (sPAP), exercise-induced pulmonary hypertension (EIPH) and the combination of EIPH and NVC grade.

(exercise sPAP > 50 mmHg) and FUPH (resting PH > 35 mmHg on echocardiography) were different from previous studies, our data confirmed that EIPH assessed by exercise echocardiography can predict the evolution of future resting sPAP. Resting sPAP as well as exercise sPAP are strong predictors of FUPH. In addition, exercise sPAP provides incremental value in predicting the onset of FUPH, and exercise echocardiography brings valuable information about the pathophysiology of the disease. Exercise echocardiography shows the consequences for the myocardium and pulmonary microvascular function. Thus, increased resting and exercise pulmonary vascular resistance in the FUPH group may suggest a pulmonary vascular impairment. Reduced myocardial microvascular function is suggested by increased estimated exercise LV filling pressure and lower exercise-induced change in LV ejection fraction, which probably corresponds to microvascular ischaemia during exercise. This hypothesis is supported by previous studies with single photon emission computed tomography assessment of myocardial perfusion, which showed ischaemia in systemic sclerosis without any coronary artery lesions [16]. Myocardial scintigraphy demonstrated evidence of reversible ischaemia together with irreversible lesions, and showed inducibility of coronary vasospasm by cold pressor provocation, suggesting both myocardial ischaemia and fibrosis [17]. Vignaux et al. [18] showed an increase in LV function and in myocardial perfusion after administration of nifedipine in patients with systemic sclerosis, suggesting a link between microvascular dynamic reserve and LV function.

Study limitations

The main limitation of our study was the low incidence of right heart catheterization to confirm resting PH in the FUPH group. Two patients had confirmed resting PH during follow-up (mPAP 26 mmHg and mPAP 33 mmHg), and one had resting mPAP during follow-up in the grey zone (mPAP 21 mmHg). However, this did not affect the main result of our study, which was that exercise echocardiography and NVC can screen patients at risk of developing FUPH. In this group, patients had a higher increase in resting sPAP during follow-up (3 ± 4.5 vs 0.4 ± 0.7 mmHg/month; $P = 0.005$), suggesting a dynamic and rapid increase in sPAP over time, corresponding to a high risk of developing resting PH.

The second limitation of our study was the relative small size of the population, but this reflects the low incidence of systemic sclerosis. Consequently, regarding the size of the population and the number of events during FU, it was not possible to perform complex multivariable analyses (including more than two variables). As age is a well-known variable influencing the level of sPAP, we decided to perform an adjustment for age in the multivariable analysis.

In addition, the timing of follow-up was determined arbitrarily, and could be modified depending on the clinical status of the patients. Therefore, the real time of onset of FUPH was not known precisely (it occurred between the time of diagnosis of FUPH and the previous echocardiographic control) and constitutes a bias for time-dependency analyses. Thus, Cox regression and Kaplan-Meier analyses should be interpreted with caution, and either linear or logistic regression may be more informative in the present case. However, even with this limitation, the results of linear and logistic regression were quite similar to time-dependency analysis results.

The small LV volumes reported could be related to foreshortening views, and may also explain the low cardiac output reported. However, this underestimation affected the whole population and, consequently, did not influence the reliability of the main result of this study, which was the demonstration that exercise sPAP and NVC grade are independent determinants of FUPH. Because of the high resting heart rate in some patients and the early fusion of E and A waves, the E/e' ratio was only available in 50% of both groups of patients. Although useful, E/e' ratio assessment during exercise seems moderately feasible and applicable in routine assessment in this particular population. It is known that pulmonary function status influences sPAP; however, there were no significant differences between patients with and without PH during follow-up for each of the lung function variables. This could be a consequence of the small population and a type II error. Patients with FUPH were significantly older, and sPAP increases with age. However, after adjustment for age and resting sPAP, both exercise sPAP and NVC grade > 2 remained significantly associated with the occurrence of PH during FU, suggesting that these two variables are independent of age and the baseline value of resting sPAP.

Finally, 15/63 (24%) patients had unquantifiable sPAP due to the absence of registrable tricuspid regurgitation, which could be a limitation to the large application of exercise echocardiography to the risk stratification of patients with systemic sclerosis. However, contrast echocardiography could be performed in these patients to increase the feasibility of the registration of the tricuspid regurgitation, and further studies should assess this point.

Conclusion

Exercise echocardiography and NVC can help us to understand the pathophysiological mechanisms leading to resting PH in patients with systemic sclerosis, and could be used

for individual risk stratification and decision making. NVC reveals the primary lesion of the disease (i.e. microvascular impairment) and echocardiography allows the assessment of the consequences of this lesion for myocardial and pulmonary vascular function. Patients with no abnormal increase in sPAP during exercise and presenting an NVC grade < 2 are at very low risk of FUPH, contrasting with patients with both EIPH and NVC grade > 2, in whom the risk of developing PH during follow-up is particularly high (82%).

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Disclosure of interest

The authors declare that they have no competing interest.

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