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Facteurs associés à la distance parcourue lors du test de marche de 6 minutes au cours de la sclérodermie systémique.

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RESUME

Contexte :

Le test de marche de 6 minutes est utilisé pour évaluer la tolérance à l'effort des patients atteints de sclérodermie systémique (SSc), notamment en cas de complications cardiopulmonaires. Cependant, ce que reflète précisément la distance parcourue lors du test (DM6) reste débattu. Notre travail vise à déterminer les facteurs associés à la DM6 chez les patients atteints de SSc (objectif principal), avec un focus sur le sous-groupe atteint de pneumopathie interstitielle diffuse (PID) (objectif secondaire).

Méthodes :

Les patients de notre Centre de Référence étaient inclus dans cette étude transversale s'ils validaient les critères ACR/EULAR 2013 de la SSc. Les données, recueillies prospectivement, comprenaient les données cliniques, les résultats du test de marche de 6 minutes, les examens biologiques (notamment hémoglobine, CRP, Nt-pro-BNP, CPK), les épreuves fonctionnelles respiratoires (EFR), l'échocardiographie transthoracique (ETT) et les scores composites (EScSG-AI, Medsger, HAQ-DI). Les associations entre la DM6 et les différentes variables étaient étudiées par régression linéaire en analyse univariée puis multivariée.

Résultats :

La population globale comprenait 298 patients. L'analyse univariée retrouvait des associations fortes avec les paramètres cardiorespiratoires (notamment classe NYHA, Nt-

pro-BNP, ETT et EFR), une association faible avec l'atteinte articulaire et pas d'association avec l'atteinte musculaire. En analyse multivariée, les paramètres indépendamment associés avec la DM6 étaient le sexe, l'âge, l'IMC, le tabagisme, la variation de fréquence cardiaque (ΔFC), la classe NYHA et la CRP. Une analyse de sensibilité incluant le score HAQ-DI montrait son association indépendante avec la DM6.

Le sous-groupe PID-SSc comprenait 113 patients. L'analyse univariée retrouvait des associations fortes avec les paramètres cardiorespiratoires, mais pas d'association avec les paramètres musculosquelettiques. En analyse multivariée, les variables indépendamment associées à la DM6 étaient le sexe, l'âge, la ΔFC et la classe NYHA. En analyse de sensibilité incluant le score HAQ-DI, celui-ci était indépendamment associé à la DM6.

Conclusion :

Au cours de la SSc, la DM6 est fortement et indépendamment associée à la ΔFC (pouvant traduire une insuffisance chronotrope s'intégrant dans une dysautonomie) et aux évaluations subjectives de limitation fonctionnelle. En revanche, nous ne retrouvons pas de relation avec l'atteinte musculosquelettique.

INTRODUCTION

Systemic sclerosis (SSc) is a rare and severe condition classified within the connective tissue disease spectrum (1). It is characterized by the progressive development of debilitating fibrosis affecting the skin and/or the internal organs, impacting on vital prognosis (2–4) and associated with functional limitation and impaired quality of life (5,6). Over the last decades, the pulmonary complications of the disease, namely pulmonary hypertension (PH) and interstitial lung disease (ILD), have become the leading cause of mortality among SSc patients (7). One of the most important objectives when managing SSc patients is therefore to detect early these complications, to properly assess their severity and to accurately follow up therapeutic efficacy.

Among the different tools available to evaluate SSc patients, the 6-minute walk test (6MWT) is simple, non-invasive, inexpensive and reproducible, and is now frequently used in daily clinical practice (8). Initially developed in the 1960s to study exercise tolerance in aviation personnel (9,10), its use has since been translated to the field of cardiopulmonary diseases (11,12), such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and idiopathic pulmonary arterial hypertension (PAH). In these mono-organ conditions, the 6-minute walk distance (6MWD) has proven to be an accurate reflection of disease severity with a prognosis significance (13–15).

However, conversely to these diseases, SSc is a systemic condition associated with various extra-pulmonary features (skin fibrosis, musculoskeletal pain, heart involvement, depression, anaemia) and with significant disability that can confound the interpretation of the 6MWT. In this multi-organ setting, the assumption that the 6MWD is an adequate

surrogate marker for the severity of cardiopulmonary complications is no longer straightforward; and this has led clinicians to wonder what is actually being measured during this test in SSc (16,17). This is of crucial importance, since the 6MWD is used in daily practice to follow up SSc patients with or without cardiopulmonary complications, and as an outcome measure in clinical trials for SSc-PAH (18–21) and ILD (22).

Several teams have tried to answer this question but their results are conflicting (23–36). For instance, forced vital capacity (FVC) measured during pulmonary function tests (PFT) was significantly associated with the 6MWD in some studies (27,29,30,33) but not in others (24,26,28,36). Similarly, associations with musculoskeletal parameters have been inconsistently observed (29,33,34). These discrepancies may arise from heterogeneous study populations and different sample sizes.

To address this issue, we performed a cross-sectional study on a large and fully phenotyped SSc patient population. Our primary objective was to assess the associations between the 6MWD and various disease characteristics in the overall SSc population. As one of the purposes of 6MWT in SSc is to detect and monitor lung complications, our secondary objective was to study these associations specifically in the subgroup of SSc patients with ILD (SSc-ILD).

METHODS

Patient selection

We designed a cross-sectional study and prospectively recruited consecutive patients over 18 years old followed in the National Referral Centre for Systemic Sclerosis of Lille from November 2014 to August 2016. They were included in the study if they fulfilled the 2013 American College of Rheumatology (ACR)/EUropean League Against Rheumatism (EULAR) classification criteria for SSc (37). There were no exclusion criteria.

The study was approved by our local institutional review board; and complied with the requirements of the French “Commission Nationale de l’Informatique et des Libertés” and with current French legislation.

Data collection

Data were prospectively collected for each patient during a comprehensive evaluation performed within a day.

Patients underwent a non-encouraged 6-minute walk test (6MWT), performed as recommended by the American Thoracic Society (ATS) (38), with measurement of total 6-minute walked distance (6MWD) in absolute value (with calculation of the relative value as previously described (39)), modified Borg score, peripheral oxygen saturation (SpO_2), blood pressure (BP) and heart rate (HR) at the beginning and the end of the test. Variation of Borg score (ΔBorg score), SpO_2 (ΔSpO_2), systolic BP (ΔsBP), diastolic BP (ΔdBP) and HR (ΔHR) were defined as the difference between the value at the end of the 6MWT and the value at the start for each parameter.

A global evaluation also recorded the following data:

- Demographics: age, sex, body mass index (BMI) and smoking history (yes/no)
- SSc characteristics: cutaneous subset according to Leroy's classification (40), disease duration, immunological profile, presence of a specific organic microangiopathy on nailfold capillaroscopy
- Main organ involvements and relevant medical history: pulmonary arterial hypertension (PAH) (defined as hemodynamically-proven pre-capillary group 1 pulmonary hypertension (41)), interstitial lung disease (ILD) (diagnosed on a chest high-resolution CT-scan and staged according to Goh's criteria (42)), digital ulcers (DU) (previously and/or at presentation), history of scleroderma renal crisis (SRC), history of acute venous thrombosis (deep vein thrombosis, pulmonary embolism) or arterial thrombosis (myocardial infarction, ischemic stroke, acute limb ischemia), history of chronic cardiovascular disease (coronary heart disease, lower extremity peripheral artery disease)
- Clinical assessment: modified Rodnan skin score (mRSS), telangiectasias, New York Heart Association (NYHA) functional score, cardiovascular symptoms (chest pain, palpitations, syncope), joint symptoms (pain or swelling), muscle symptoms (pain or weakness)
- Biological data: haemoglobin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinin and glomerular filtration rate (GFR) estimated by the Modification of Diet in Renal Disease (MDRD) equation, Nt-pro-BNP, creatinin kinase (CK), ferritin, serum complement (total haemolytic activity (CH50), complement fraction 3 (C3) and 4 (C4))
- Transthoracic echocardiography (TTE): left ventricular ejection fraction (LVEF), left ventricular diastolic function, aortic and mitral valves status, peak tricuspid regurgitation

velocity (TRV), estimated systolic pulmonary artery pressure (sPAP), right atrial (RA) area, inferior vena cava (IVC) diameter and collapse, pericardial status

- Pulmonary function tests (PFT): total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume during the first second (FEV1), FEV1 to FVC ratio (FEV1/FVC), diffusing capacity of the lung for carbon monoxide (DLCO), diffusing coefficient for carbon monoxide (KCO)
- Composite scores: European Scleroderma Study Group Activity Index (EScSG-AI) (43), Medsger severity score (44), Health Assessment Questionnaire-Disability Index (HAQ-DI) (45)

Statistical analyses

Characteristics of the population were described using mean ± standard deviation (SD) for quantitative variables, and number (n), percentage (%) for qualitative variables. Characteristics of patients with and without ILD were compared using *t*-tests for quantitative variables and Fisher's exact tests for qualitative variables.

In order to study the associations between the 6MWD (in absolute value) as the dependant variable and the various explanatory variables, we first conducted univariate analyses using linear regressions. Results were expressed using crude (non-adjusted) coefficients [95% confidence interval (CI)], expressed in meters. Variables associated with the 6MWD in univariate analyses were then selected based on the *p*-value (set at 0.10 for the overall population analysis and at 0.20 for the ILD subgroup analysis) and introduced in a multivariate linear regression model. Variables were excluded from the analysis in case of colinearity or large amount of missing data (TTE). As composite scores were associated with several other variables, they were also excluded from the main multivariate analyses but were inserted in a separate regression model as sensitivity

analyses. Results were expressed using adjusted coefficients [95% CI], expressed in meters. Regression diagnostics were performed.

All statistical analyses were performed using R software, version 3.2.5 (46). The threshold for statistical significance was set to $p < 0.05$.

RESULTS

Patient characteristics

Overall, the study population comprised 298 patients (*Table 1*). Most of them were middle-aged females (sex-ratio m/f = 0.23; mean age = 58.2 ± 13.3 years old) with a limited cutaneous SSc (82.2%) associated with anti-centromere antibodies (56.0%). ILD (41.2%) and DU (43.0%) were the most frequent complications of the disease, while PAH (5.9%) and SRC (0.35%) remained rare. During the 6MWT, patients walked a mean distance of 438.3 ± 108.1 m (81.6 ± 17.8% of the predicted value), decreased their SpO_2 of a mean 0.58 ± 2.72% and increased their HR of a mean 10.4 ± 11.2 bpm.

SSc-ILD patients were mostly classified as NYHA classes I-II (72.6%) and as limited ILD (71.1%) according to Goh's criteria. They displayed moderate PFT alterations (mean FVC = 91.7 ± 23.5%; mean DLCO = 60.0 ± 19.6%). The SSc-ILD subset featured a higher proportion of patients with diffuse cutaneous SSc (93.0% *vs*. 65.5% respectively, $p<10^{-6}$; mean mRSS = 6.71 ± 6.77 *vs*. 4.12 ± 5.29 respectively, $p<10^{-3}$), anti-topoisomerase I antibodies (40.4% *vs*. 7.8%, $p<10^{-6}$) and PAH (11.1% *vs*. 3.3% respectively, $p=0.02$) when compared to patients without ILD (SSc-no ILD). During the 6MWT, SSc-ILD patients walk a similar distance (431.0 ± 110.0 m *vs*. 436.4 ± 111.5 m, $p=0.67$) but reached lower final SpO_2 values (96.7 ± 4.1 *vs*. 97.8 ± 2.8% respectively, $p= 0.009$) and higher final Borg scores (2.8 ± 2.1 *vs*. 2.3 ± 2.2 respectively, $p= 0.02$) than SSc-no ILD patients.

Table 1. Characteristics of the study population (overall and as a function of interstitial lung disease).

	Overall SSc		SSc-no ILD		SSc-ILD		
	N	Value	N	Value	N	Value	*p**
Demographic data							
Females, n (%)	298	242 (81.2)	157	136 (86.6)	113	81 (71.7)	0.003
Age at inclusion (years), mean (SD)	298	58.2 (13.3)	157	56.9 (12.7)	113	60.0 (14.1)	0.04
BMI (kg/m^2), mean (SD)	283	24.9 (5.3)	149	25.3 (5.3)	107	24.2 (5.1)	0.06
Smoking history, n (%)	297	119 (40.1)	157	68 (43.3)	112	38 (33.9)	0.13
Diagnosis of SSc							
SSc subtype							
lcSSc, n (%)	298	245 (82.2)	157	146 (93.0)	113	74 (65.5)	$<10^{-6}$
dcSSc, n (%)	298	53 (17.8)	157	11 (7.0)	113	39 (34.5)	$<10^{-6}$
Disease duration at inclusion							
Since diagnosis (years), mean (SD)	298	9.1 (8.1)	157	9.1 (8.1)	113	9.9 (8.0)	0.38
Since first non-Raynaud symptom (years), mean (SD)	244	9.9 (8.5)	123	10.7 (9.1)	97	9.6 (7.8)	0.54
Since Raynaud phenomenon onset (years), mean (SD)	279	15.6 (12.2)	147	16.7 (11.7)	106	15.3 (12.9)	0.16
Immunological profile							
Anti-centromere antibodies, n (%)	291	163 (56.0)	154	110 (71.4)	109	33 (30.3)	$<10^{-6}$
Anti-topoisomerase I antibodies, n (%)	291	57 (19.6)	154	12 (7.8)	109	44 (40.4)	$<10^{-6}$
Anti-RNA polymerase III antibodies, n (%)	291	7 (2.4)	154	7 (4.6)	109	0 (0.0)	0.04
Anti-RNP antibodies, n (%)	291	15 (5.2)	154	10 (6.5)	109	5 (4.6)	0.60
Nailfold capillaroscopy							
Specific organic microangiopathy, n (%)	109	98 (89.9)	57	56 (98.3)	37	29 (78.4)	0.002
History of organ involvments							
Interstitial lung disease, n (%)	270	113 (41.9)	157	0 (0.0)	113	113 (100.0)	/
Limited ILD, n (%)	97	69 (71.1)	/	/ /	97	69 (71.1)	/
Extensive ILD, n (%)	97	28 (28.9)	/	/ /	97	28 (28.9)	/
PID duration at inclusion (years), mean (SD)	93	7.0 (5.8)	/	/ /	93	7.0 (5.8)	/
Pulmonary arterial hypertension, n (%)	286	17 (5.9)	152	5 (3.3)	108	12 (11.1)	0.02
Digital ulcers (previously or at inclusion), n (%)	298	128 (43.0)	157	60 (38.2)	113	59 (52.2)	0.03

Scleroderma renal crisis, n (%)	285	1	(0.4)	148	0	(0.0)	110	1	(0.9)	0.43
Acute venous thrombosis, n (%)	297	33	(11.1)	157	20	(12.7)	112	11	(9.8)	0.56
Acute arterial thrombosis, n (%)	297	27	(9.1)	156	16	(10.3)	113	11	(9.7)	1.00
Chronic cardiovascular disease, n (%)	296	21	(7.1)	155	11	(7.1)	113	10	(8.9)	0.65
Clinical evaluation at inclusion										
Modified Rodnan skin score, mean (SD)	297	4.96	(5.95)	156	4.12	(5.29)	113	6.71	(6.77)	$<10^{-3}$
Telangiectasias, n (%)	275	199	(72.4)	145	113	(77.9)	107	68	(63.6)	0.02
NYHA functional class										
Class I, n (%)	296	132	(44.6)	155	77	(49.7)	113	35	(31.0)	0.005
Class II, n (%)	296	101	(34.1)	155	48	(31.0)	113	47	(41.6)	0.005
Class III, n (%)	296	57	(19.3)	155	29	(18.7)	113	26	(23.0)	0.005
Class IV, n (%)	296	6	(2.0)	155	1	(0.7)	113	5	(4.4)	0.005
Cardiovascular symptoms, n (%)	298	24	(8.1)	157	19	(12.1)	113	4	(3.5)	0.01
Joint symptoms, n (%)	296	125	(42.2)	157	73	(46.5)	111	39	(35.1)	0.08
Muscle symptoms, n (%)	297	57	(19.2)	157	30	(19.1)	112	21	(18.8)	1.00
6 minute walk test										
Total distance (m), mean (SD)	298	438.3	(108.1)	157	436.4	(111.5)	113	431.0	(110.0)	0.67
Total distance (% predicted), mean (SD)	290	81.6	(17.8)	151	80.4	(17.7)	111	80.7	(18.4)	0.83
Initial SpO_2 (%), mean (SD)	280	98.1	(2.1)	150	98.3	(1.6)	104	97.7	(2.8)	0.24
Final SpO_2 (%), mean (SD)	275	97.5	(3.3)	148	97.8	(2.8)	101	96.7	(4.1)	0.009
ΔSpO_2 (%), mean (SD)	276	-0.58	(2.72)	148	-0.43	(2.76)	101	-0.98	(2.92)	0.01
Initial Borg score, mean (SD)	294	0.4	(1.1)	155	0.4	(1.0)	111	0.6	(1.3)	0.27
Final Borg score, mean (SD)	294	2.5	(2.2)	155	2.3	(2.2)	111	2.8	(2.1)	0.02
ΔBorg score, mean (SD)	293	2.1	(1.9)	154	2.0	(2.0)	111	2.3	(1.8)	0.06
Inital sBP (mmHg), mean (SD)	292	123.8	(16.6)	155	123.6	(16.5)	109	123.4	(17.0)	0.82
Final sBP (mmHg), mean (SD)	292	132.9	(18.2)	155	132.4	(18.7)	109	132.7	(16.9)	0.93
ΔsBP (mmHg), mean (SD)	291	9.2	(14.0)	154	8.8	(14.5)	109	9.3	(13.0)	0.81
Inital dBP (mmHg), mean (SD)	271	97.4	(3.4)	146	97.8	(2.9)	99	96.6	(4.2)	0.008
Final dBP (mmHg), mean (SD)	292	73.6	(10.0)	155	72.9	(10.3)	109	73.7	(9.3)	0.71
ΔdBP (mmHg), mean (SD)	291	0.95	(10.2)	154	0.31	(10.5)	109	2.3	(9.7)	0.15
Initial HR (bpm), mean (SD)	289	76.7	(12.3)	155	76.0	(11.0)	108	77.2	(14.4)	0.80

Final HR (bpm), mean (SD)	288	87.1	(15.9)	155	85.1	(13.6)	107	88.7	(18.7)	0.14
ΔHR (bpm), mean (SD)	288	10.4	(11.2)	155	9.1	(10.0)	107	11.5	(12.2)	0.13
Biological data										
Haemoglobin (g/dL), mean (SD)	291	13.4	(1.4)	154	13.4	(1.3)	111	13.2	(1.6)	0.29
ESR (mm/h), mean (SD)	258	14.8	(15.3)	137	14.4	(14.4)	97	15.7	(17.2)	0.92
CRP (mg/L), mean (SD)	293	4.0	(4.7)	154	3.4	(3.9)	112	4.8	(5.7)	0.01
Creatinin (mg/L), mean (SD)	294	8.0	(2.8)	155	7.9	(2.2)	112	8.3	(3.6)	0.30
Estimated GFR (mL/min/1.73m^2), mean (SD)	294	89.1	(21.5)	155	88.4	(20.6)	112	89.6	(24.3)	0.90
Nt-pro-BNP (pg/mL), mean (SD)	290	266.0	(623.7)	153	208.3	(619.0)	110	378.6	(682.2)	0.01
CK (UI), mean (SD)	289	93	(59.5)	155	93.3	(48.8)	108	88.3	(48.7)	0.27
Ferritin (ng/mL), mean (SD)	268	105.5	(136.4)	140	112.2	(146.2)	103	99.7	(136.1)	0.55
Complement activation, n (%)	265	9	(3.4)	143	5	(3.5)	98	4	(4.1)	1.00
Transthoracic echocardiography										
Left ventricular ejection fraction (%), mean (SD)	184	63.1	(6.4)	107	62.8	(5.8)	57	62.6	(7.3)	0.83
Left ventricular diastolic dysfunction, n (%)	174	22	(12.6)	102	13	(12.8)	52	8	(15.4)	0.63
Valvular heart disease, n (%)	187	43	(23.0)	109	18	(16.5)	58	22	(37.9)	0.004
Peak TRV (m/s), mean (SD)	142	2.49	(0.55)	82	2.46	(0.45)	45	2.62	(0.73)	0.64
Estimated sPAP (mmHg), mean (SD)	153	32.4	(13.6)	88	30.2	(10.4)	51	37.1	(18.3)	0.08
Right atrial area (cm^2), mean (SD)	107	15.2	(4.3)	56	14.9	(4.2)	38	16.2	(4.6)	0.13
IVC dilation, n (%)	152	7	(4.6)	88	1	(1.1)	51	6	(11.8)	0.01
Decreased IVC collapse, n (%)	132	7	(5.3)	69	1	(1.5)	49	6	(12.2)	0.02
Pericardial effusion, n (%)	180	7	(3.9)	104	2	(1.9)	57	4	(7.0)	0.19
Pulmonary function tests										
TLC (% predicted), mean (SD)	276	96.2	(16.4)	145	102.0	(11.3)	105	86.5	(18.5)	$<10^{-6}$
FVC (% predicted), mean (SD)	287	103.5	(21.8)	152	109.7	(16.8)	108	91.7	(23.5)	$<10^{-6}$
FEV1 (% predicted), mean (SD)	286	95.1	(21.8)	151	99.6	(18.2)	108	85.5	(22.7)	$<10^{-6}$
FEV1/FVC (%), mean (SD)	286	79.2	(10.7)	151	78.3	(9.2)	108	80.0	(12.1)	0.22
DLCO (% predicted), mean (SD)	285	70.0	(19.7)	152	74.8	(16.6)	106	59.8	(19.6)	$<10^{-6}$
KCO (% predicted), mean (SD)	278	80.9	(17.6)	148	81.6	(16.4)	104	77.8	(18.2)	0.10
Composite scores										
EScSG-AI score, mean (SD)	289	1.16	(1.2)	151	0.95	(1.0)	110	1.60	(1.5)	$<10^{-3}$

Medsger severity score, mean (SD)	228	4.17	(2.5)	119	3.64	(2.3)	86	5.33	(2.3)	$<10^{-6}$
HAQ-DI score, mean (SD)	223	0.61	(0.7)	118	0.62	(0.6)	81	0.71	(0.7)	0.57

BMI: body mass index; CK: creatin kinase; CRP: C-reactive protein; dBP: diastolic blood pressure; dc: diffuse cutaneous; DLCO: diffusing capacity of the lung for carbon monoxide; EScSG-AI: European Scleroderma Study Group Activity Index; ESR: erythrocyte sedimentation rate; FEV1: forced expiratory volume during the first second; FVC: forced vital capacity; GFR: glomerular filtration rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; HR: heart rate; ILD: interstitial lung disease; IVC: inferior vena cava; KCO: diffusing coefficient for carbon monoxide; lc: limited cutaneous; n: number; NYHA: New York Heart Association; sBP: systolic blood pressure; SD: standard deviation; sPAP: systolic pulmonary arterial pressure; SpO_2: peripheral oxygen saturation; SSc: systemic sclerosis; TLC: total lung capacity; TRV: tricuspid regurgitation velocity; Δ: variation of.

*p-values for comparison between SSc-no ILD and SSc-ILD groups.

Associations with the 6-minute walk distance in the global SSc population

Univariate analyses revealed several associations between the 6MWD and the collected parameters (*Table 2*).

Regarding general patient and SSc characteristics, the 6MWD was associated with gender ($p<10^{-3}$), age ($p<10^{-6}$), BMI ($p<10^{-6}$), smoking habits ($p=0.01$), disease duration ($p=0.02$) and PAH ($p<10^{-6}$). There was no association with the cutaneous subset, with other SSc complications (especially ILD: $p=0.69$), and with immunological profile.

Regarding cardiopulmonary parameters, we found significant strong associations of the 6WMD with NYHA functional class ($p<10^{-6}$ for all stages, with a dose-effect attested by the increase in β-values from class II to class IV), cardiovascular symptoms ($p=0.03$), Nt-pro-BNP levels ($p<10^{-3}$), echocardiographic markers of PH (especially estimated sPAP: $p<10^{-3}$) and left-heart dysfunction (LVEF: $p=0.03$; diastolic dysfunction: $p=0.008$), and PFT results (including TLC: $p=0.007$; and DLCO: $p<10^{-3}$). Other cardiopulmonary parameters measured during the 6MWT also displayed significant associations with the total distance, especially ΔBorg score ($p<10^{-6}$) and ΔHR ($p<10^{-3}$).

Regarding extra-cardiopulmonary parameters, we observed an association with articular involvement (joint symptoms: $p=0.02$), but no association with markers of musculoskeletal (muscular symptoms: $p=0.08$; CK levels: $p=0.11$) and skin (mRSS: $p=0.74$; DU: $p=0.25$) involvements.

Regarding global indicators of disease activity and severity, the 6MWD was significantly and strongly associated with haemoglobin ($p<10^{-6}$), ESR ($p<10^{-6}$), CRP ($p<10^{-3}$), EScSG-AI ($p=0.001$) and Medsger severity scores ($p<10^{-3}$). We also found a markedly large association of the 6MWD with the HAQ-DI score ($p<10^{-6}$).

Table 2. Associations between 6MWD and SSc characteristics: univariate analyses in the overall SSc population.

	β	[95%CI]	*p*
Male (*vs*. female)	52.7	[21.8; 83.6]	$<10^{-3}$
Age (per 1-year increment)	-3.6	[-4.5; -2.8]	$<10^{-6}$
BMI (per 1 kg/m^2 increment)	-4.1	[-6.4; -1.7]	$<10^{-3}$
Smoking history (*vs*. no history)	31.8	[6.9; 56.7]	0.01
lcSSc (*vs*. dcSSc)	0.7	[-31.5; 32.8]	0.97
Disease duration since diagnosis (per 1-year increment)	-1.8	[-3.3; -0.3]	0.02
Disease duration since first non-RP symptom (per 1-year increment)	-2.3	[-3.8; -0.7]	0.004
Disease duration since RP onset (per 1-year increment)	-1.2	[-2.2; -0.2]	0.02
ACA (*vs*. no ACA)	-23.4	[-48.1; 1.3]	0.06
ATA (*vs*. no ATA)	0.1	[-31.0; 31.3]	0.99
ARA (*vs*. no ARA)	47.2	[-33.2; 127.7]	0.25
Anti-RNP antibodies (*vs*. no anti-RNP antibodies)	3.7	[-52.2; 59.5]	0.90
Abnormal nailfold capillaroscopy (*vs*. normal)	-18.1	[-86.7; 50.6]	0.61
ILD (*vs*. no ILD)	-5.4	[-32.2; 21.4]	0.69
PAH (*vs*. no PAH)	-131.8	[-183.2; -80.3]	$<10^{-6}$
DU (previously or at inclusion) (*vs*. no DU)	19.1	[-13.4; 51.5]	0.25
History of scleroderma renal crisis (*vs*. no history)	-41.3	[-250.8; 168.3]	0.70
History of venous thrombosis (*vs*. no history)	-65.0	[-103.6; -26.5]	0.001
History of arterial thrombosis (*vs*. no history)	-58.9	[-101.3; -16.5]	0.007
History of cardiovascular disease (*vs*. no history)	-103.8	[-150.2; -57.5]	$<10^{-3}$
Modified Rodnan skin score (per 1-point increment)	-0.4	[-2.4; 1.7]	0.74
Telangiectasia (*vs*. no telangiectasia)	-12.4	[-41.0; 16.1]	0.39
NYHA class II (*vs*. class I)	-76.1	[-100.1; -52.2]	$<10^{-6}$
NYHA class III (*vs*. class I)	-132.1	[-160.8; -103.3]	$<10^{-6}$
NYHA class IV (*vs*. class I)	-227.4	[-303.1; -151.7]	$<10^{6}$
Cardiovascular symptoms (*vs*. no symptoms)	-49.8	[-94.6; -4.9]	0.03
Joint symptoms (*vs*. no symptoms)	-29.4	[-54.3; -4.6]	0.02
Muscle symptoms (*vs*. no symptoms)	-27.8	[-58.9; 3.4]	0.08
Initial SpO_2 (per 1% increment)	14.9	[9.2; 20.7]	$<10^{-6}$
Final SpO_2 (per 1% increment)	9.1	[5.4; 12.8]	$<10^{-3}$
ΔSpO_2 (per 1% increment)	4.7	[0.0; 9.4]	0.05
Initial Borg score (per 1-point increment)	-22.5	[-33.3; -11.7]	$<10^{-3}$
Final Borg score (per 1-point increment)	-17.7	[-23.0; -12.4]	$<10^{-6}$
ΔBorg score (per 1-point increment)	-15.9	[-22.1; -9.6]	$<10^{-6}$
Inital sBP (per 1 mmHg increment)	-1.0	[-1.7; -0.2]	0.01
Final sBP (per 1 mmHg increment)	-0.6	[-1.2; 0.1]	0.11
ΔsBP (per 1 mmHg increment)	0.4	[-0.5; 1.3]	0.37
Inital dBP (per 1 mmHg increment)	9.1	[5.3; 12.8]	$<10^{-3}$
Final dBP (per 1 mmHg increment)	0.5	[-0.7; 1.8]	0.42
ΔdBP (per 1 mmHg increment)	0.6	[-0.7; 1.8]	0.36
Initial HR (per 1 bpm increment)	-1.9	[-2.9; -0.9]	$<10^{-3}$
Final HR (per 1 bpm increment)	-0.1	[-0.9; 0.7]	0.86
ΔHR (per 1 bpm increment)	2.1	[1.0; 3.2]	$<10^{-3}$
Haemoglobin (per 1 g/dL increment)	26.6	[18.0; 35.2]	$<10^{-6}$

ESR (per 1 mm/h increment)	-2.3	[-3.1; -1.5]	$<10^{-6}$
CRP (per 1 mg/L increment)	-5.8	[-8.4; -3.2]	$<10^{-3}$
Creatinin (per 1 mg/L increment)	-3.6	[-8.0; 0.8]	0.11
Estimated GFR (per 1 mL/min/1.73m^2 increment)	1.1	[0.6; 1.7]	$<10^{-3}$
Nt-pro-BNP (per 1 pg/mL increment)	0.0	[-0.1; 0.0]	$<10^{-3}$
CK (per 1 IU increment)	0.2	[0.0; 0.4]	0.11
Ferritin (per 1 ng/mL increment)	0.0	[-0.1; 0.1]	0.55
Complement activation (*vs*. no activation)	1.6	[-70.0; 73.3]	0.96
LVEF (per 1% increment)	2.9	[0.3; 5.5]	0.03
LVDD (*vs*. no LVDD)	-67.2	[-116.6; -17.8]	0.008
Valvular heart disease (*vs*. no valvular heart disease)	-65.1	[-102.9; -27.2]	$<10^{-3}$
Peak TRV (per 1 m/s increment)	-58.7	[-91.8; -25.6]	$<10^{-3}$
Estimated sPAP (per 1 mmHg increment)	-2.8	[-4.1; -1.5]	$<10^{-3}$
Right atrial area (per 1 cm^2 increment)	-4.2	[-8.8; 0.4]	0.07
IVC dilation (*vs*. no IVC dilation)	-59.0	[-142.6; 24.5]	0.17
Decreased IVC collapse (*vs*. normal IVC collapse)	-106.9	[-187.9; -25.9]	0.01
Pericardial effusion (*vs*. no pericardial effusion)	-39.4	[-126.2; 47.3]	0.37
TLC (per 1% increment)	1.0	[0.3; 1.8]	0.007
FVC (per 1% increment)	0.4	[-0.2; 0.9]	0.20
FEV1 (per 1% increment)	0.3	[-0.3; 0.9]	0.29
FEV1/FVC (per 1% increment)	0.8	[-0.3; 2.0]	0.16
DLCO (per 1% increment)	1.4	[0.8; 2.0]	$<10^{-3}$
KCO (per 1% increment)	0.7	[0.0; 1.5]	0.04
EScSG-AI score (per 1-point increment)	-16.4	[-26.2; -6.5]	0.001
Medsger severity score (per 1-point increment)	-10.8	[-66.8; -24.2]	$<10^{-3}$
HAQ-DI score (per 1-point increment)	-104.6	[-122.0; -87.2]	$<10^{-6}$

6MWD: 6-minute walk distance; ACA: anti-centromere antibodies; ARA: anti-RNA polymerase III antibodies; ATA: anti-topoisomerase I antibodies; BMI: body mass index; CI: confidence interval; CK: creatin kinase; CRP: C-reactive protein; dBP: diastolic blood pressure; dc: diffuse cutaneous; DLCO: diffusing capacity of the lung for carbon monoxide; DU: digital ulcers; EScSG-AI: European Scleroderma Study Group Activity Index; ESR: erythrocyte sedimentation rate; FEV1: forced expiratory volume during the first second; FVC: forced vital capacity; GFR: glomerular filtration rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; HR: heart rate; ILD: interstitial lung disease; IU: international unit; LVDD: left ventricular diastolic dysfunction; LVEF: left ventricular ejection fraction; IVC: inferior vena cava; KCO: diffusing coefficient for carbon monoxide; lc: limited cutaneous; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; RP: Raynaud phenomenon; sBP: systolic blood pressure; sPAP: systolic pulmonary arterial pressure; SpO_2: peripheral oxygen saturation; SSc: systemic sclerosis; TLC: total lung capacity; TRV: tricuspid regurgitation velocity; Δ: variation of.

Based on the results of the univariate analyses, we built a multivariate model to determine the factors independently associated with the 6MWD (*Table 3*). The only parameters that were significantly and independently associated with 6MWD were gender (β=72.0 [40.3;103.8] m for men *vs.* women, $p<10^{-3}$), age (β=-3.0 [-4.1;-2.0] m per increment of 1 year, $p<10^{-6}$), BMI (β=-3.5 [-5.8;-1.3] m per increment of 1 kg/m^2, p=0.002), smoking history (β=-24.3 [-47.9;-0.7] m for ever-smokers *vs.* never-smokers, p=0.04), NYHA class (β-values from -30.3 [-57.7;-3.1] m for class II to -155.5 [-247.0;-63.9] m for class IV *vs.* class I, $p<10^{-3}$), ΔHR (β=2.8 [1.8;3.8] m per increment of 1 bpm, $p<10^{-6}$), and CRP (β=-3.5 [-6.0;-1.0] m per increment of 1 mg/L, p=0.007). There was also a trend for an association with haemoglobin (β=8.4 [-0.3;17.1] m per increment of 1 g/dL; p=0.06) and Nt-pro-BNP (β=-0.02 [-0.05;0.00] m per increment of 1 pg/mL; p=0.06).

As the HAQ-DI score was associated with several other variables, it was not inserted our main multivariate regression but studied in a separate model as a sensitivity analysis. This revealed a significant and independent association of the HAQ-DI score with the 6MWD (β=-56.1 [-83.8;-28.4] m per increment of 1 unit, $p<10^{-3}$) (data not shown).

Table 3. Associations between 6MWD and SSc characteristics: multivariate analysis in the overall SSc population.

N=200	β	[95%CI]	*p*
Male (*vs*. female)	72.0	[40.2; 103.8]	$<10^{-3}$
Age (per 1-year increment)	-3.0	[-4.1; -1.9]	$<10^{-6}$
BMI (per 1 kg/m^2 increment)	-3.5	[-5.8; -1.3]	0.002
Smoking history (*vs*. no history)	-24.3	[-47.8; -0.7]	0.04
Disease duration since diagnosis (per 1-year increment)	0.8	[-0.7; 2.3]	0.30
ACA (*vs*. no ACA)	-1.2	[-24.7; 22.4]	0.92
PAH (*vs*. no PAH)	33.9	[-40.5; 108.4]	0.37
History of venous thrombosis (*vs*. no history)	-16.6	[-55.3; 22.2]	0.40
History of arterial thrombosis (*vs*. no history)	-5.9	[-44.3; 32.5]	0.76
NYHA class (*vs*. class I)			$<10^{-3}$
Class II	-30.4	[-57.7; -3.1]	
Class III	-75.3	[-108.9; -41.6]	
Class IV	-155.5	[-247.0; -63.9]	
Cardiovascular symptoms (*vs*. no symptoms)	-18.3	[-57.5; 20.9]	0.36
Joint symptoms (*vs*. no symptoms)	-2.9	[-26.6; 20.8]	0.81
Muscle symptoms (*vs*. no symptoms)	13.0	[-15.6; 41.6]	0.37
Initial SpO_2 (per 1% increment)	2.3	[-4.2; 8.7]	0.49
ΔSpO_2 (per 1% increment)	2.8	[-2.1; 7.7]	0.26
ΔBorg score (per 1-point increment)	-3.0	[-9.6; 3.7]	0.38
Inital sBP (per 1 mmHg increment)	0.0	[-0.8; 0.8]	0.99
Initial HR (per 1 bpm increment)	-0.9	[-1.8; 0.1]	0.08
ΔHR (per 1 bpm increment)	2.8	[1.8; 3.8]	$<10^{-6}$
Haemoglobin (per 1 g/dL increment)	8.4	[-0.3; 17.1]	0.06
CRP (per 1 mg/L increment)	-3.5	[-6.0; -1.0]	0.007
Estimated GFR (per 1 mL/min/1.73m^2 increment)	0.2	[-0.3; 0.7]	0.42
Nt-pro-BNP (per 1 pg/mL increment)	0.0	[-0.1; 0.0]	0.06
TLC (per 1% increment)	-0.1	[-1.0; 0.9]	0.90
DLCO (per 1% increment)	0.2	[-0.6; 1.0]	0.60

R^2 for this model is 0.64.

6MWD: 6-minute walk distance; ACA: anti-centromere antibodies; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; GFR: glomerular filtration rate; HR: heart rate; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; sBP: systolic blood pressure; SpO_2: peripheral oxygen saturation; SSc: systemic sclerosis; TLC: total lung capacity; Δ: variation of.

Associations with the 6-minute walk distance in the SSc-ILD subgroup

Similarly to the overall SSc population, univariate analyses were conducted to assess associations between the 6MWD and each of the collected parameters, and yielded similar results (*Table 4*).

Regarding general patient and SSc characteristics, the 6MWD was here again associated with gender (p=0.02), age ($p<10^{-3}$), disease duration (p=0.04) and PAH ($p<10^{-3}$). There was no influence of the cutaneous subset, immunological profile and other SSc complications.

Regarding cardiopulmonary parameters, we observed significant associations with NYHA functional class ($p<10^{-3}$ for all stages, here again with a dose-effect), Nt-pro-BNP levels (p=0.002), echocardiographic markers of PH (including estimated sPAP: $p<10^{-3}$), and PFT results (especially DLCO: $p<10^{-3}$). The 6MWD was also associated with most of the other cardiopulmonary parameters measured during the test, including ΔBorg score (p=0.001), but not ΔHR (p=0.19).

Regarding extra-cardiopulmonary parameters, we did not find any significant association between the 6MWD and joint symptoms (p=0.24), muscle symptoms (p=0.27), CK levels (p=0.06), mRSS (p=0.68) or DU (p=0.23).

Regarding global disease activity and severity assessments, there were significant associations with haemoglobin ($p<10^{-3}$), ESR ($p<10^{-3}$) and CRP (p=0.02), but not with EScSG-AI score (p=0.13), and Medsger severity score (p=0.11). Here again, the HAQ-DI score was strongly associated with the 6MWD ($p<10^{-6}$).

Table 4. Associations between 6MWD and SSc characteristics: univariate analyses in the SSc-ILD subgroup.

	β	[95%CI]	*p*
Male (*vs*. female)	53.3	[9.1; 97.4]	0.02
Age (per 1-year increment)	-3.4	[-4.7; -2.1]	$<10^{-3}$
BMI (per 1 kg/m^2 increment)	-2.3	[-6.4; 1.8]	0.27
Smoking history (*vs*. no history)	33.6	[-9.3; 76.4]	0.13
lcSSc (*vs*. dcSSc)	-18.6	[-61.3; 24.1]	0.39
Disease duration since diagnosis (per 1-year increment)	-0.6	[-3.2; 1.9]	0.63
Disease duration since first non-RP symptom (per 1-year increment)	-1.6	[-4.5; 1.3]	0.28
Disease duration since RP onset (per 1-year increment)	-1.7	[-3.3; -0.1]	0.04
ACA (*vs*. no ACA)	-32.6	[-77.3; 12.1]	0.16
ATA (*vs*. no ATA)	1.1	[-41.2; 43.4]	0.96
Anti-RNP antibodies (*vs*. no anti-RNP antibodies)	24.6	[-74.4; 123.7]	0.63
Abnormal nailfold capillaroscopy (*vs*. normal)	-25.0	[-101.4; 51.4]	0.52
PAH (*vs*. no PAH)	-117.4	[-180.9; -54.0]	$<10^{-3}$
DU (previously or at inclusion) (*vs*. no DU)	29.0	[-17.8; 75.9]	0.23
History of scleroderma renal crisis (*vs*. no history)	-34.4	[-251.8; 183.0]	0.76
History of venous thrombosis (*vs*. no history)	-97.1	[-163.8; -30.5]	0.005
History of arterial thrombosis (*vs*. no history)	-73.1	[-140.4; -5.7]	0.04
History of cardiovascular disease (*vs*. no history)	-98.0	[-167.4; -28.6]	0.007
Modified Rodnan skin score (per 1-point increment)	-0.6	[-3.6; 2.4]	0.68
Telangiectasia (*vs*. no telangiectasia)	-16.8	[-60.6; 27.0]	0.45
NYHA class II (*vs*. class I)	-74.2	[-113.1; -35.3]	$<10^{-3}$
NYHA class III (*vs*. class I)	-155.5	[-200.6; -110.4]	$<10^{-6}$
NYHA class IV (*vs*. class I)	-236.1	[-319.4; -152.9]	$<10^{-6}$
Cardiovascular symptoms (*vs*. no symptoms)	-59.9	[-169.6; 49.8]	0.29
Joint symptoms (*vs*. no symptoms)	-25.9	[-69.0; 17.2]	0.24
Muscle symptoms (*vs*. no symptoms)	-29.6	[-81.8; 22.6]	0.27
Initial SpO_2 (per 1% increment)	10.3	[3.0; 17.5]	0.007
Final SpO_2 (per 1% increment)	7.1	[2.1; 12.1]	0.006
ΔSpO_2 (per 1% increment)	4.4	[-2.9; 11.7]	0.24
Initial Borg score (per 1-point increment)	-17.0	[-32.7; -1.4]	0.03
Final Borg score (per 1-point increment)	-19.3	[-28.3; -10.4]	$<10^{-3}$
ΔBorg score (per 1-point increment)	-18.3	[-29.2; -7.5]	0.001
Inital sBP (per 1 mmHg increment)	-1.3	[-2.5; -0.1]	0.03
Final sBP (per 1 mmHg increment)	-1.0	[-2.2; 0.2]	0.12
ΔsBP (per 1 mmHg increment)	0.6	[-1.0; 2.2]	0.45
Inital dBP (per 1 mmHg increment)	7.0	[2.0; 12.1]	0.008
Final dBP (per 1 mmHg increment)	-0.5	[-2.8; 1.7]	0.64
ΔdBP (per 1 mmHg increment)	1.3	[-0.9; 3.4]	0.25
Initial HR (per 1 bpm increment)	-1.4	[-2.9; 0.0]	0.05
Final HR (per 1 bpm increment)	-0.4	[-1.5; 0.8]	0.52
ΔHR (per 1 bpm increment)	1.2	[-0.6; 2.9]	0.19
Haemoglobin (per 1 g/dL increment)	25.1	[12.5; 37.7]	$<10^{-3}$
ESR (per 1 mm/h increment)	-2.1	[-3.3; -0.9]	$<10^{-3}$
CRP (per 1 mg/L increment)	-4.3	[-7.9; -0.8]	0.02

Creatinin (per 1 mg/L increment)	-1.4	[-7.1; 4.3]	0.63
Estimated GFR (per 1 mL/min/1.73m^2 increment)	1.1	[0.3; 1.9]	0.01
Nt-pro-BNP (per 1 pg/mL increment)	0.0	[-0.1; 0.0]	0.002
CK (per 1 IU increment)	0.4	[0.0; 0.9]	0.06
Ferritin (per 1 ng/mL increment)	0.0	[-0.2; 0.1]	0.70
Complement activation (*vs*. no activation)	21.4	[-89.3; 132.2]	0.71
LVEF (per 1% increment)	0.1	[-4.1; 4.3]	0.95
LVDD (*vs*. no LVDD)	-29.8	[-119.0; 59.5]	0.52
Valvular heart disease (*vs*. no valvular heart disease)	-18.5	[-79.6; 42.6]	0.56
Peak TRV (per 1 m/s increment)	-65.1	[-107.8; -22.3]	0.005
Estimated sPAP (per 1 mmHg increment)	-3.5	[-5.0; -2.0]	$<10^{-3}$
Right atrial area (per 1 cm^2 increment)	-9.4	[-16.5; -2.2]	0.01
IVC dilation (*vs*. no IVC dilation)	-55.7	[-148.9; 37.5]	0.25
Decreased IVC collapse (*vs*. normal IVC collapse)	-102.3	[-194.3; -10.2]	0.03
Pericardial effusion (*vs*. no pericardial effusion)	-37.6	[-154.8; 79.6]	0.53
TLC (per 1% increment)	1.0	[-0.1; 2.1]	0.08
FVC (per 1% increment)	0.8	[0.0; 1.7]	0.06
FEV1 (per 1% increment)	1.0	[0.1; 1.8]	0.04
FEV1/FVC (per 1% increment)	1.0	[-0.7; 2.7]	0.24
DLCO (per 1% increment)	2.0	[1.0; 3.0]	$<10^{-3}$
KCO (per 1% increment)	1.4	[0.2; 2.5]	0.02
EScSG-AI score (per 1-point increment)	-10.8	[-24.6; 2.9]	0.13
Medsger severity score (per 1-point increment)	-8.1	[-17.9; 1.7]	0.11
HAQ-DI score (per 1-point increment)	-108.8	[-132.0; -85.5]	$<10^{-6}$

6MWD: 6-minute walk distance; ACA: anti-centromere antibodies; ARA: anti-RNA polymerase III antibodies; ATA: anti-topoisomerase I antibodies; BMI: body mass index; CI: confidence interval; CK: creatin kinase; CRP: C-reactive protein; dBP: diastolic blood pressure; dc: diffuse cutaneous; DLCO: diffusing capacity of the lung for carbon monoxide; DU: digital ulcers; EScSG-AI: European Scleroderma Study Group Activity Index; ESR: erythrocyte sedimentation rate; FEV1: forced expiratory volume during the first second; FVC: forced vital capacity; GFR: glomerular filtration rate; HAQ-DI: Health Assessment Questionnaire-Disability Index; HR: heart rate; ILD: interstitial lung disease; IU: international unit; LVDD: left ventricular diastolic dysfunction; LVEF: left ventricular ejection fraction; IVC: inferior vena cava; KCO: diffusing coefficient for carbon monoxide; lc: limited cutaneous; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; RP: Raynaud phenomenon; sBP: systolic blood pressure; sPAP: systolic pulmonary arterial pressure; SpO_2: peripheral oxygen saturation; SSc: systemic sclerosis; TLC: total lung capacity; TRV: tricuspid regurgitation velocity; Δ: variation of.

Using results from univariate analyses, we next proceeded to build a multivariate model in the same way we did for the overall population (*Table 5*). The only parameters that were significantly and independently associated with 6MWD were gender (β=50.8 [0.80;100.9] m for men *vs.* women, *p*=0.05), age (β=-2.76 [-4.47;-1.05] m per increment of 1 year, *p*=0.002), NYHA class (β-values from -31.3 [-77.9;15.3] m for class II to -141.6 [-250.9;-32.4] m for class IV *vs.* class I, *p*=0.004), ΔHR (β=2.28 [0.54;4.02] m per increment of 1 bpm, *p*=0.01); and a trend for a significant association with haemoglobin (β=11.0 [-1.9;24.0] m per increment of 1 g/dL; *p*=0.09). A sensitivity analysis including the HAQ-DI score revealed an independent association with the 6MWD (β=-57.2 [-101.8;-12.6] m per increment of 1 unit, *p*=0.01) (data not shown).

Table 5. Associations between 6MWD and SSc characteristics: multivariate analysis in the SSc-ILD subgroup.

N=78	β	[95%CI]	*p*
Male (*vs*. female)	50.8	[0.8; 100.9]	0.05
Age (per 1-year increment)	-2.8	[-4.5; -1.0]	0.002
Smoking history (*vs*. no history)	-0.9	[-45.2; 43.5]	0.97
Disease duration since RP onset (per 1-year increment)	0.8	[-0.9; 2.6]	0.34
ACA (*vs*. no ACA)	4.0	[-42.6; 50.6]	0.86
PAH (*vs*. no PAH)	-1.8	[-84.8; 81.2]	0.97
History of venous thrombosis (*vs*. no history)	-29.2	[-115.1; 56.7]	0.50
History of arterial thrombosis (*vs*. no history)	-35.0	[-98.4; 28.5]	0.27
NYHA class (*vs*. class I)			0.004
Class II	-31.3	[-77.9; 15.3]	
Class III	-96.0	[-152.2; -39.8]	
Class IV	-141.6	[-250.8; -32.4]	
Initial SpO_2 (per 1% increment)	-1.5	[-9.6; 6.6]	0.71
ΔBorg score (per 1-point increment)	-10.5	[-23.0; 2.0]	0.10
Inital sBP (per 1 mmHg increment)	-0.3	[-1.6; 1.0]	0.61
Initial HR (per 1 bpm increment)	-0.3	[-1.9; 1.2]	0.65
ΔHR (per 1 bpm increment)	2.3	[0.5; 4.0]	0.01
Hemoglobin (per 1 g/dL increment)	11.0	[-1.9; 23.9]	0.09
CRP (per 1 mg/L increment)	-0.8	[-4.7; 3.0]	0.66
Estimated GFR (per 1 mL/min/1.73m^2 increment)	0.3	[-0.6; 1.1]	0.52
Nt-pro-BNP (per 1 pg/mL increment)	0.0	[-0.1; 0.0]	0.38
FVC (per 1% increment)	-0.7	[-1.9; 0.5]	0.25
DLCO (per 1% increment)	0.9	[-0.4; 2.2]	0.16

R^2 for this model is 0.70.

6MWD: 6-minute walk distance; ACA: anti-centromere antibodies; CI: confidence interval; CRP: C-reactive protein; DLCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity; GFR: glomerular filtration rate; HR: heart rate; NYHA: New York Heart Association; RP: Raynaud phenomenon; PAH: pulmonary arterial hypertension; sBP: systolic blood pressure; SpO_2: peripheral oxygen saturation; SSc: systemic sclerosis; Δ: variation of.

DISCUSSION

In this cross-sectional study, we tried to identify the factors associated with the 6MWD in a large and fully characterized population of SSc patients. We conducted our analyses in the overall SSc population as well as in the SSc-ILD subgroup, and found the following results: (1) aside from usual demographic parameters, we observed significant and independent associations of the 6MWD with ΔHR and NYHA functional class in both populations (as well as with CRP in the overall SSc group); (2) in sensitivity analyses, when included in the models, the HAQ-DI score was also independently associated with the 6MWD in both populations.

Although data in the literature are conflicting, the results of our univariate analyses confirm findings from several previous works, which observed associations of the 6MWD with demographic (age and BMI) and cardiopulmonary parameters (especially PFT and TTE), but no major influence of musculoskeletal involvement (23–36). Multivariate analyses from previous studies have also established age (24), gender (26), dyspnoea (24,26), HAQ scores (29) and CRP (27) as independent factors associated with the 6MWD. Conversely, we did not observe any independent association with DLCO (26,29,36) and initial or final SpO_2 (26) as reported before, which might be explained by heterogeneity between study populations.

Association of the 6MWD with ΔHR

Association between the 6MWD and ΔHR has never been studied before in SSc. In the overall SSc population, an increase of 1 bpm from initial HR was associated with a mean increase of 2.9 [1.8;3.8] m in the 6MWD. Interestingly, similar findings were made in IPF (47) and PAH [45] patients, where the variation in HR was found to be an important factor associated with the 6MWD as well as valuable prognosis marker.

Interpretation of this result in the context of the 6MWT, a submaximal non-incremental exercise test, is challenging. On the one hand, the lower increase in HR observed in some SSc patients could simply indicate lower exercise intensity due to limited functional capacities (49). On the other hand, it could also reflect an actual impairment of the chronotropic response to exercise. Chronotropic incompetence, defined as the inability to increase HR above 80% of its predicted peak value during a maximal exercise test, is indeed a major cause of exercise intolerance in various cardiopulmonary diseases (49–51). As the mechanisms underlying this condition involve an imbalance between the sympathetic and parasympathetic regulation of HR, it is a common finding in patients with heart diseases (sick sinus syndrome, atrial fibrillation, ischemic heart disease, chronic heart failure), neurological disorders (through autonomic dysfunction) or specific medication intakes (such as β-blockers and non-dihydropyridine calcium-channel inhibitors) (49,50,52).

Since the 6MWT is a submaximal exercise test, the diagnosis of chronotropic incompetence cannot be made here with certainty; and since detailed patient history and medications were not readily available, the causes for the impaired chronotropic response in our population cannot be fully investigated. However, it is interesting to note that autonomic dysfunction is increasingly recognized as a frequent complication of SSc (53,54), especially in terms of cardiac involvement and heart rate regulation (55–58). One hypothesis could thus be that an impaired chronotropic response could be an independent

factor associated with exercise intolerance in SSc. This result warrants further investigations and could open the way to a specific management of SSc patients in order to improve their exercise tolerance.

Association of the 6MWD with HAQ-DI score and NYHA functional class

Another interesting finding of our study is the associations observed between the 6MWD and two distinct measurements of functional limitation: the NYHA score in the main multivariate models and the HAQ-DI score in the sensitivity analyses.

In a previous study, Deuschle *et al.* observed a significant association between the 6MWD and the NYHA functional class in univariate regression, and showed that a walk distance below 477m identified patients in classes III-IV (29). Although often used a staging system for dyspnoea severity, the NYHA classification was initially developed as a measure of functional capacities in heart diseases (59). Interestingly, studies have casted doubts regarding what information is actually captured by this classification (symptom severity, functional performance and/or psychosocial status), especially when patient-assessed (60,61).

Similarly, several teams have also found associations between the 6MWD and the HAQ-DI score, both in univariate and multivariate regression (29,31). Remarkably, in a previous work, Chow *et al.* showed that the HAQ-DI score was not associated with parameters of cardiopulmonary severity in SSc patients with PAH (62). This implies that the patient perception of disability and functional limitation is not entirely explained by the actual gravity of the disease.

Overall, these results suggest that the 6MWD should probably be interpreted as an overall assessment of disability and quality of life rather than a severity marker for specific organ involvements.

Association of the 6MWD with CRP

An independent association between CRP levels and the 6WWD was observed in the overall SSc population. A similar result was also found in a previous work by Schoindre *et al*. (27) both in univariate and multivariate regressions, but not by Deuschle *et al*. (29). Interestingly, CRP levels are associated with EScSG-AI score, Medgser severity score, HAQ-DI score and with a poor prognosis in SSc patients (63,64). In line with our prior results, this observation could suggest that the 6MWD also captures the overall disease activity and severity. This could explain why 6MWD was shown to poorly reflect hemodynamic severity in SSc-associated PAH (65).

Lack of independent association between the 6MWD and objective markers of lung severity in our SSc-ILD population

Although associations with PFT or Nt-pro-BNP levels were found in univariate analyses, none of the objective markers of lung severity was independently associated with the 6MWD, notably in the SSc-ILD subgroup. NYHA functional class was among the independent factor associated with the 6MWD in this patient subset; however, as detailed above, whether this relation reflects the actual gravity of the pulmonary disease remains uncertain. Overall, these results suggest that lung involvement severity may not have a straightforward influence on the 6MWD in our population of SSc-ILD patients.

Lack of interference of the musculoskeletal involvement in the 6MWD

Contrary to a common idea (17), it is interesting to note that musculoskeletal involvement is not independently associated with the 6MWD in both our study populations. The effect of joint and muscle symptoms have been previously suggested in univariate analyses (29,33,34) but has never been tested in a multivariate analysis. Interestingly, quadricipital strength and joint involvement have been found to correlate both with the

6MWD and with the HAQ-DI score in SSc patients (33,34,66), which suggests that this score may also account for the musculoskeletal-induced disability impacting on the 6MWD.

Our study draws strength from a large sample size, an important number of tested variables and the prospective collection of data. It also has limitations, notably an important number of missing data regarding echocardiographic parameters. This has prevented us from inserting them in our multivariate models, making us unable to assess whether their association with the 6MWD was independent.

In conclusion, our work showed that, aside from demographic parameters, heart rate variation and global disability (as assessed by NYHA functional class or HAQ-DI score) are important factors associated with the 6MWD in SSc. This suggests that the 6MWD should be interpreted as a global assessment of disease activity and patient disability rather than a surrogate marker for specific organ involvements (whether cardiorespiratory or musculoskeletal). Further studies are warranted to investigate the possibility of a chronotropic incompetence as a cause for exercise intolerance in SSc patients.

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Date de Soutenance : 28 Octobre 2016
Titre de la Thèse : Facteurs associés à la distance parcourue lors du test de marche de 6 minutes au cours de la sclérodermie systémique.

Thèse - Médecine - Lille 2016
Cadre de classement : Médecine interne
DES + spécialité : Médecine interne
Mots-clés : sclérodermie systémique, pneumopathie interstitielle diffuse, test de marche de 6 minutes, insuffisance chronotrope, incapacité

Résumé :

Contexte : Le test de marche de 6 minutes est utilisé pour évaluer la tolérance à l'effort des patients atteints de sclérodermie systémique (SSc), notamment en cas de complications cardiopulmonaires. Cependant, ce que reflète précisément la distance parcourue lors du test (DM6) reste débattu. Notre travail vise à déterminer les facteurs associés à la DM6 chez les patients atteints de SSc (objectif principal), avec un focus sur le sous-groupe atteint de pneumopathie interstitielle diffuse (PID) (objectif secondaire).

Méthodes : Les patients de notre Centre de Référence étaient inclus dans cette étude transversale s'ils validaient les critères ACR/EULAR 2013 de la SSc. Les données, recueillies prospectivement, comprenaient les données cliniques, les résultats du test de marche de 6 minutes, les examens biologiques (notamment hémoglobine, CRP, Nt-pro-BNP, CPK), les épreuves fonctionnelles respiratoires (EFR), l'échocardiographie transthoracique (ETT) et les scores composites (EScSG-AI, Medsger, HAQ-DI). Les associations entre la DM6 et les différentes variables étaient étudiées par régression linéaire en analyse univariée puis multivariée.

Résultats : La population globale comprenait 298 patients. L'analyse univariée retrouvait des associations fortes avec les paramètres cardiorespiratoires (notamment classe NYHA, Nt-pro-BNP, ETT et EFR), une association faible avec l'atteinte articulaire et pas d'association avec l'atteinte musculaire. En analyse multivariée, les paramètres indépendamment associés avec la DM6 étaient le sexe, l'âge, l'IMC, le tabagisme, la variation de fréquence cardiaque (ΔFC), la classe NYHA et la CRP. Une analyse de sensibilité incluant le score HAQ-DI montrait son association indépendante avec la DM6. Le sous-groupe PID-SSc comprenait 113 patients. L'analyse univariée retrouvait des associations fortes avec les paramètres cardiorespiratoires, mais pas d'association avec les paramètres musculosquelettiques. En analyse multivariée, les variables indépendamment associées à la DM6 étaient le sexe, l'âge, la ΔFC et la classe NYHA. En analyse de sensibilité incluant le score HAQ-DI, celui-ci était indépendamment associé à la DM6.

Conclusion : Au cours de la SSc, la DM6 est fortement et indépendamment associée à la ΔFC (pouvant traduire une insuffisance chronotrope s'intégrant dans une dysautonomie) et aux évaluations subjectives de limitation fonctionnelle. En revanche, nous ne retrouvons pas de relation avec l'atteinte musculosquelettique.

Composition du Jury :
Président : Pr Pierre-Yves Hatron
Assesseurs : Pr Éric Hachulla, Dr Pascal de Groote, Dr Jean-François Bervar, Pr David Launay (directeur de thèse)