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Exercise pulmonary haemodynamics predict outcome in patients with systemic sclerosis

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ABSTRACT The aim of the present study was to investigate the prognostic value of exercise haemodynamics measured during right heart catheterisation (RHC) in patients with systemic sclerosis (SSc) referred for evaluation of pulmonary hypertension.

SSc patients undergoing RHC at rest and during maximal supine incremental cycle exercise were grouped into resting precapillary pulmonary hypertension (PH_{rest}) (mean pulmonary artery pressure (mPAP) ⩾25 mmHg, pulmonary artery wedge pressure <15 mmHg), exercise-induced pulmonary hypertension (PH_{ex}) (mPAP ⩾30 mmHg and mPAP/cardiac output >3 $mmHg \cdot L^{-1} \cdot min^{-1}$ at maximal exercise), and without pulmonary hypertension (PH_{none}). Patients' characteristics, haemodynamics and follow up data were compared between groups.

72 SSc patients were followed for median (interquartile range) 33 (15–55) months. Mean (95% CI) survival without transplantation estimated by Kaplan–Meyer analysis was 4.4 (0.8–2.9) years in PH_{rest} (n=17), 5.2 (4.4–6.1) years in PH_{ex} (n=28) and 9.5(8.4–10.6) years in PH_{none} (n=27; p<0.05 *versus* others). In Cox regression models, the exercise-induced increase in mPAP (hazard ratio (HR) 1.097, 95% CI 1.002–1.200) and the coefficient of pulmonary vascular distensibility alpha (HR 0.100, 95% CI 0.012–0.871) controlled for age, but not resting haemodynamics predicted transplant-free survival.

Among SSc patients with normal mPAP at rest, an excessive increase in mPAP during exercise and an impaired vascular distensibility may indicate an early stage of pulmonary vasculopathy, associated with reduced survival similar to resting pulmonary hypertension patients.

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Introduction

Pulmonary arterial hypertension (PAH) is a common and severe complication in patients with connective tissue disease [1, 2]. In particular, PAH is most frequent in systemic sclerosis (SSc) with an estimated prevalence of 7.5–12% [3–5] and it is the leading cause of death in SSc with almost one-third of SSc-related deaths [6–9].

The gold standard for diagnosis of PAH in SSc patients is right heart catheterisation (RHC) and PAH is defined as precapillary pulmonary hypertension with a mean pulmonary artery pressure (mPAP) ⩾25 mmHg with a pulmonary artery wedge pressure (PAWP) ⩽15 mmHg at rest [10]. Exercise pulmonary hypertension, defined by mPAP >30 mmHg during exercise, has been eliminated as a diagnostic criterion for pulmonary hypertension due to lack of agreement on a cut-off value for exercise pulmonary hypertension, with insufficient supporting data in the literature and missing specification of this criterion on the exact exercise level, type and posture [11]. While mPAP at rest has been found to be age-independent in healthy individuals, mPAP during exercise appeared to frequently exceed 30 mmHg at high cardiac output (CO) during exercise, especially in individuals aged ⩾50 years [12]. Nevertheless, an exercise-induced increase in mPAP will most probably be a precursor of resting pulmonary hypertension in patients at risk, such as in those with SSc. Thus, more research is needed to define the clinical relevance and outcome of patients with exercise-induced pulmonary hypertension in this patient population [13–15]. Recently, Hervé *et al.* [16] found that a combined maximum mPAP >30 mmHg and total pulmonary vascular resistance (TPVR) >3 WU during exercise was associated with pulmonary vascular disease independent of age, sex, body mass index and diagnosis.

As PAH associated with SSc is a prevalent and potentially fatal condition for which treatment is available, it is important to identify those SSc patients who are at high risk of having early pulmonary vascular disease with the intent to delay or even prevent deterioration. The aim of this study was therefore to review exercise RHC performed at our centre in SSc patients and to study the prognostic value of exercise pulmonary haemodynamics in terms of transplant-free survival and to compare it with established markers of disease severity.

Methods

Study design and patients

Data on all SSc patients who had diagnostic RHC at our pulmonary hypertension-referral centre due to clinical suspicion of pulmonary hypertension (exertional dyspnoea and/or unclearly reduced diffusing capacity of the lung for carbon monoxide (*D*LCO) or a forced vital capacity (FVC)/*D*LCO >1.6) were reviewed. It has been our clinical practice since September 2005 to perform supine incremental cycle ergometry during RHC in all patients with precapillary pulmonary hypertension unless they are unstable or suffer from musculoskeletal problems precluding cycling. SSc patients were censored in November 2015. Patients with postcapillary pulmonary hypertension, defined as PAWP >15 mmHg at rest or >20 mmHg during exercise, and patients with other pulmonary hypertension classification (FVC <60% predicted or other aetiology of pulmonary hypertension than SSc) were excluded from the study [17].

Available chest computed tomography was reviewed and scored for the percentage of lung volume with fibrosis with 0:none, 1: <20%; and 2: >20%. Demographics, clinical classification of SSc as limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc) or not classified SSc, WHO functional class (WHO–FC), 6-min walk distance (6MWD), pulmonary function, echocardiography and venous and arterial blood test results were recorded [18]. Follow-up data including WHO–FC, 6MWD, haemodynamics by echocardiography and *N*-terminal pro-brain natriuretic peptide (NT-proBNP) from the regular visits every 3–6 months up to 2 years after the RHC were analysed until occurrence of an event (defined as death or lung transplantation) or until November 2015 in censored patients. PAH-specific medication consisting of endothelin-receptor antagonists (ERA) or phosphodiesterase-5-inhibitors (PDE-5-inhibitors) given during follow-up for >3 months was noted. All patients gave their written informed consent to have their data registered and the study was approved by the local ethical review board (KEK 2012-0125).

Exercise RHC

A balloon-tipped, triple-lumen, fluid-filled 7.5 Fr Swan Ganz catheter (Baxter/Edwards, Deerfield, IL, USA) was introduced *via* an internal jugular vein [19]. Transducers were set at the mid-axillary line and zeroed to atmospheric pressure [20, 21]. Cardiac output was assessed by continuous thermodilution (Baxter/Edwards) and cardiac output/body surface area yielded the cardiac index (CI). The pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were calculated as: PVR=(mPAP −PAWP)/cardiac output; SVR=(mPAP−RAP)/cardiac output, the transpulmonary gradient (TPG)=mPAP −PAWP. Mean baseline measurements after 15 min of rest were noted as resting values. Supine cycling exercise was performed according a symptom-limited, stepwise incremental protocol starting with 10 Watt followed by increase of 10 Watt every 3 min (TheraVital, Medica GmbH, Ravensburg) at a cycle rate of

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60 revolutions·min^{-1}. Measurements were taken during the last 30 s of each step. Pulmonary artery distensibility index α was calculated as previously described [19, 22].

SSc patients were allocated to three different groups according to their resting and exercise haemodynamics: 1) resting precapillary pulmonary hypertension (mPAP⩾25 mmHg, PAWP ⩽15 mmHg) (PHrest); 2) exercise precapillary pulmonary hypertension (mPAP at maximal exercise >30 mmHg with a mPAP/cardiac output >3 mmHg·min·L^{-1}, PAWP <20 mmHg) (PHex) [16]; and 3) patients without pulmonary hypertension (PHnone).

Statistical analysis

Data are summarised by medians (interquartile range) for continuous values in order to account for some non-normally distributed values and frequencies (%) for binary and categorical variables. Baseline variables by groups were compared using Mann–Whitney U-test or Fisher's exact test when appropriate. Follow-up comparisons were calculated using the Wilcoxon test. Transplant-free survival was calculated by Kaplan–Meier analysis with comparisons of the time to event performed by log-rank test. Cox regression was used for predictors of transplant-free survival. A two-sided p-value <0.05 was considered as significant throughout. SPSS 22 (SPSS, Chicago, IL, USA) was used.

Results

Baseline characteristics

From 84 exercise-RHC performed in SSc, 12 patients had postcapillary pulmonary hypertension at rest or exercise and were excluded (figure 1). From the 72 eligible patients, 17 (24%) had PHrest, 28 (39%) had PHex, 27 (38%) had PHnone. Demographic and clinical data by haemodynamic groups are shown in table 1. The majority was female with lcSSc, history of Raynaud, an impaired *D*LCO and anti-centromere antibodies-positive, irrespective of the subgroup. At baseline, patients with PHrest were significantly older and had a worse WHO–FC than PHex and PHnone (table 1). The 6MWD was significantly shorter in patients with PHrest (394 (324–478) m) compared with PHex (489 (357–565) m) (p=0.030) and PHnone (492 (365–558) m) (p=0.040). There was no difference in FVC % predicted/*D*LCO % predicted ratio amongst the groups, although PHrest tended to have a higher ratio. Five out of 11 with PHrest had pulmonary fibrosis (four out of five <20%), four out of 19 with PHex had fibrosis (three out of four <20%) and three out of 17 with PHnone had fibrosis (two out of three <20%). Serum analysis showed higher levels of NT-proBNP for PHrest compared with PHex and PHnone. Targeted treatment for PAH was introduced in all patients with PHrest and off-label by judgments of the treating physicians in 16 (57%) patients with PHex and consisted of ERA and/or PDE-5-inhibitors.

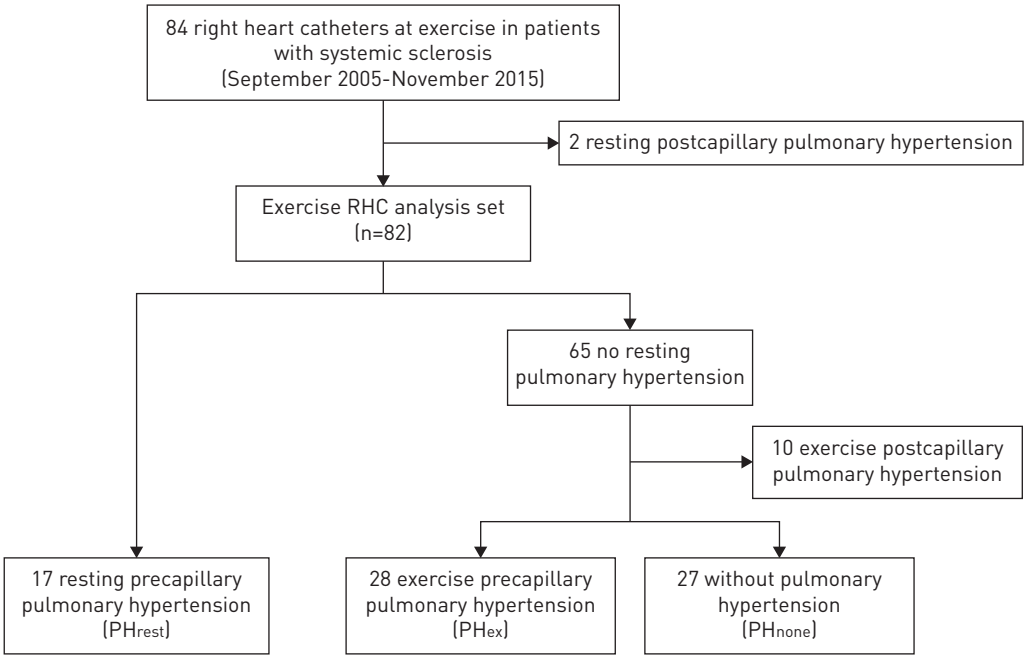

FIGURE 1 The haemodynamic classification of 84 patients with systemic sclerosis who were investigated with exercise right heart catheterisation are shown. RHC: right heart catheter; PH: pulmonary hypertension.

TABLE 1 Characteristics of systemic sclerosis patients according to their haemodynamic classification into resting pulmonary hypertension (PH_{rest}), pulmonary hypertension during exercise (PH_{ex}) and without pulmonary hypertension (PH_{none})

Variable	Patient groups		
	PH_{rest}	PH_{ex}	PH_{none}
Patients	17 (20)	28 (33)	27 (32)
Demographical parameters			
Female	12 (71)*	24 (86)	26 (94)
Age years	66 (59–70)*	63 (54–74)¶¶	51 (42–65)
Clinical parameters			
WHO–FC	3 (2–3)**,##	2 (2–3)¶¶	2 (1–2)
I/II	5 (29)*,##	17 (61)	21 (77)
III/IV	12 (71)	10 (39)	5 (19)
BMI kg·m^{-2}	24.5 (20.3–27.2)	25.4 (23.4–28.2)	23.1 (19.9–27.2)
Exercise capacity			
6MWD m	394 (324–478)*,##	489 (357–565)	492 (365–558)
S_{pO_2} after 6MWD %	94 (87–96)	94 (87–96)¶¶	96 (92–98)
Heart rate after 6MWD beats·min^{-1}	106 (92–135)	110 (98–125)	116 (100–135)
Pulmonary function			
FEV_1 % predicted	77 (68–87)	84 (67–101)	93 (81–105)
TLC % predicted	87 (79–100)	97 (83–109)	97 (83–108)
FVC % predicted	80 (69–91)*,##	93 (83–110)	96 (83–106)
D_{LCO} % predicted	38 (35–68)	59 (45–63)	59 (50–65)
FVC % predicted/D_{LCO} % predicted	2.0 (1.3–2.5)	1.7 (1.5–2)	1.6 (1.4–1.9)
Blood analysis			
Antinuclear anti-body positive	17 (100)	28 (100)	27 (100)
Anti-Scl-70 positive	2 (12)	4 (28)¶¶	11 (41)
Anti-centromere positive	7 (41)	9 (32)¶¶	10 (37)
NT-proBNP ng·L^{-1}	500 (276–1360)*,##	153 (74–428)	132 (68–362)
Echocardiography			
Left ventricular ejection fraction %	63 (60–69)	63 (62–65)	62 (58–65)
Right atrium area cm^2	20 (15–24)*,##	16 (15–17)	14 (13–18)
Tricuspid regurgitation velocity m·s^{-1}	3.2 (2.8–3.9)**,##	2.6 (2.5–2.9)	2.2 (2.2–2.9)
Treatment			
Targeted treatment for pulmonary hypertension	17 (100)	16 (57)	0 (0)

Data are presented as n (%) or median (interquartile range). WHO–FC: World Health Organization functional class; BMI: body mass index; 6MWD: 6-min walk distance; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; NT-proBNP: *N*-terminal-pro brain natriuretic peptide. *: p<0.05 PH_{rest} to PH_{none}; **: p<0.001 PH_{rest} to PH_{none}; ##: p<0.001 PH_{rest} to PH_{ex}; ¶¶: p<0.001 PH_{ex} to PH_{none}.

Haemodynamics

Per definition, patients with PH_{rest} and PH_{ex} had higher mPAP, TPG and PVR at rest and during exercise compared with PH_{none} (p<0.001 in all comparisons; table 2). In PH_{rest}, median mPAP was 30 (26–43) mmHg at rest and 50 (45–62) mmHg at maximal workload, whereas in PH_{ex} mPAP was significantly lower at rest (20 (17–21)) mmHg and increased to 33 (31–36) mmHg (p=0.000). Patients with PH_{rest} achieved a lower maximal workload than patients with PH_{none}, the difference to PH_{ex} was not significant. Increase of mPAP during exercise was greater in PH_{rest} with 17 (11–23) mmHg and PH_{ex} with 14 (13–16) mmHg compared with PH_{none} 7 (4.5;9) mmHg (p=0.000). The pressure–flow ratio (mPAP/cardiac output) was lowest in PH_{none} (3.7 (1.7–7.9)), intermediate in PH_{ex} (8.2 (6.1–30)) and highest in PH_{rest} (24 (12.6–82.2) (all p<0.05). Arterial oxygen saturation (S_{aO_2}) was significantly lower in PH_{rest} compared with PH_{ex} (p=0.009) and PH_{none}.

Functional assessments during follow-up

All patients who received target treatment for PAH were followed up after 3, 12 and 24 months (table 3). Over the observation period, the number of treated patients with WHO–FC III or IV decreased in PH_{rest} from 12 (71%) at baseline to two (40%) after 24 months and in treated PH_{ex} from six (38%) to one (17%). Physical performance assessed by 6MWD improved in PH_{rest} from 394 (324–478) m to 476 (370–593) m and in PH_{ex} with PAH target treatment from 506 (357–570) m to 520 (386–560) m (not significant).

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TABLE 2 Haemodynamics of systemic sclerosis patients according to their haemodynamic classification into resting pulmonary hypertension (PH_{rest}), pulmonary hypertension during exercise (PH_{ex}) and without pulmonary hypertension (PH_{none})

Variable	Patient groups		
	PH_{rest}	**PH_{ex}**	**PH_{none}**
Resting haemodynamics			
HR beats·min^{-1}	79 (69–93)	72 (63–78)	75 (68–81)
mBP mmHg	101 (89–113)$^{*,\#}$	89 (81–105)	89 (82–99)
mPAP mmHg	30 (26–43)$^{**,\#\#}$	20 (17–21)¶¶	16 (14–18)
PAWP mmHg	12 (10–13)$^{*,\#}$	10 (8–12)	9 (7–11)
RAP mmHg	8 (5–9)$^{*,\#}$	8 (4–8)	5 (4–8)
TPG mmHg	20 (16–25)$^{**,\#\#}$	9 (8–12)¶	7 (6–8)
CI L·min^{-1}·m^{-2}	2.9 (2.3–3.6)	3.3 (2.7–3.9)	3.2 (2.8–3.6)
CO L·min^{-1}	5.1 (3.7–6.4)	5.6 (4.4–6.9)	5.3 (4.4–6.7)
PVR WU	3.6 (2.9–6.1)$^{***,\#\#}$	1.6 (1.3–2.2)¶	1.3 (0.9–1.7)
Sa_{O_2} %	91 (89–94)$^{**,\#}$	95 (92–95)	95 (93–96)
Sv_{O_2} %	68 (62–70)$^{*,\#}$	71 (67–72)	71 (69–74)
Exercise haemodynamics			
Maximal workload W	20 (15–30)*	30 (20–40)	30 (30–40)
Maximal HR beats·min^{-1}	111 (101–126)	111 (99–123)	104 (100–120)
Maximal mBP mmHg	110 (99–127)*	111 (97–118)¶	99 (89–109)
Maximal mPAP mmHg	50 (45–62)$^{**,\#\#}$	33 (31–36)¶¶	24 (21–25)
Maximal PAWP mmHg	15 (11–17)*	16 (14–19)¶¶	11 (7–14)
Maximal RAP mmHg	10 (8–18)$^{**,\#}$	8 (5–10)¶	5 (2–6)
Maximal TPG mmHg	34 (26–44)$^{**,\#\#}$	19 (16–21)¶¶	12 (10–16)
Maximal CI L·min^{-1}·m^{-2}	3.5 (2.6–4.3)	4.2 (3.6–4.8)	3.9 (3.5–4.8)
Maximal CO L·min^{-1}	6.2 (4.1–7.4)$^{\#}$	7.1 (6.6–8.1)	6.9 (5.8–8.9)
Maximal PVR WU	5.4 (3.8–10)$^{**,\#\#}$	2.7 (2–3.1)¶	1.7 (1.0–2.1)
Maximal Sa_{O_2} %	91 (84–95)$^{**,\#}$	95 (89–96)	96 (95–97)
Maximal Sv_{O_2} %	43 (36–54)	47 (42–54)	49 (44–55)
ΔmPAP/ΔCO mmHg·min·L^{-1}	24 (15–81)$^{**,\#}$	9.4 (6–27)¶¶	3.7 (2–7)
Increase of mPAP with exercise mmHg	18 (12–24)**	14 (13–16)¶¶	7 (5–9)
Increase mPAP per Watt mmHg·W^{-1}	0.8 (0.5–1.2)$^{**,\#}$	0.6 (0.3–0.8)¶¶	0.2 (0.1–0.3)
Distensibility index α %·mmHg^{-1}	0.5 (0.2–0.6)$^{**,\#\#}$	0.7 (0.6–0.8)¶¶	1.2 (0.9–1.6)

Data are presented as median (interquartile range). HR: heart rate; mBP: mean blood pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; RAP: right atrial pressure; TPG: transpulmonary gradient; CI: cardiac index; CO: cardiac output; PVR: pulmonary vascular resistance; Sa_{O_2}: oxygen saturation (by radial artery blood gas analysis at rest and finger-tip or earlobe pulse-oximetry during exercise); Sv_{O_2}: mixed venous oxygen saturation. *: p<0.05 PH_{rest} to PH_{none}; **: p<0.001 PH_{rest} to PH_{none}; #: p<0.05 PH_{rest} to PH_{ex}; ##: p<0.001 PH_{rest} to PH_{ex}; ¶: p<0.05 PH_{ex} to PH_{none}; ¶¶: p<0.001 PH_{ex} to PH_{none}.

TABLE 3 Follow-up of patients who received pulmonary arterial hypertension targeted medical therapy after 3, 12 and 24 months

	PH_{rest}			**PH_{ex} with treatment**		
	Baseline	**3 months**	**12 months**	**Baseline**	**3 months**	**12 months**
WHO–FC	2 (2–3)	3 (2–3)	2 (2–3)	2 (2–3)	2 (2–2)	2 (2–3)
I/II	5 (29)	6 (43)	4 (67)	10 (63)	11 (79)	7 (64)
III/IV	12 (71)	8 (57)	2 (33)	6 (38)	3 (21)	4 (36)
6MWD	394 (324–478)	456 (331–480)	464 (416–595)	506 (357–570)	517 (386–563)	517 (364–630)
Sp_{O_2} after 6MWD %	94 (87–96)	87 (86–95)	90 (89–96)	93 (87–96)	95 (94–97)	92 (85–97)
HR after 6MWD beats·min^{-1}	106 (92–135)	108 (88–125)	121 (89–132)	104 (96–122)	114 (100–132)	108 (89–129)
NT-proBNP ng·L^{-1}	500 (276–1360)	329 (251–823)	477 (287–965)	111 (64–233)	164 (98–293)	239 (90–860)
Tricuspid regurgitation velocity m·s^{-1}	3.2 (2.8–3.9)		3 (2.9–3.9)	2. (2.5–2.8)		2.6 (2.5–2.7)
Right atrium area cm^2	18 (17–21)		20 (16–22)	15 (13–17)		16 (13–19)

Data are presented as median (interquartile range) or n (%). WHO–FC: World Health Organization functional class; 6MWD: 6-min walk distance; Sp_{O_2}: arterial oxygen saturation measured by pulse oximetry; HR: heart rate; NT-proBNP: *N*-terminal pro-brain natriuretic peptide.

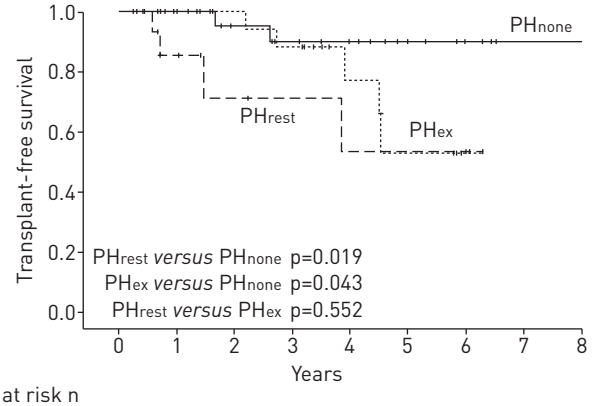
Survival

Ten patients died during the median follow-up period of 33 (13–55) months, three (18%) with PH_{rest}, five (18%) with PH_{ex} and two (7%) with PH_{none}. Death was related to progressive right heart failure in seven patients (three in PH_{rest}, four in PH_{ex}), to respiratory tract infections in one patient (PH_{none}), to multiorgan disease with microangiopathy of the kidney in one patient (PH_{none}) and to a psychiatric disorder in one patient (PH_{ex}). In three out of four PH_{ex} patients who died with right heart failure, 2.8–2.6 years after diagnosis, progression to resting pulmonary hypertension could be documented by echocardiography 12–22 months after the RHC. One patient with progressive PH_{ex} and one with PH_{rest} underwent lung transplantation. The 1-, 3- and 5-year event-free survivals were 88%, 82% and 77% for PH_{rest}, 100%, 93% and 82% for PH_{ex} and 100%, 93% and 93% for PH_{none}, respectively. Mean (95% CI) survival without transplantation by Kaplan–Meyer was 4.4 (0.8–2.9) years in PH_{rest} (n=17), 5.2 (4.4–6.1) years in PH_{ex} (n=28) and 9.5 (8.4–10.6) years in PH_{none} and significantly better in PH_{none} *versus* PH_{rest} (p=0.019) or PH_{ex} (p=0.043) (figure 2). No difference in transplant-free survival could be found in PH_{rest} *versus* PH_{ex} or patients with PH_{ex} who were treated *versus* untreated. Univariate cox-regression revealed WHO–FC, NT-proBNP blood levels, FVC/D_{LCO} ratio, mPAP at maximal exercise or increase during exercise, increase mPAP per Watt, pulmonary vascular distensibility index α, resting mixed-venous oxygen saturation (S_{vO_2}) and oxyhaemoglobin as predictors of transplant-free survival in the SSc-patient collective (table 4). Resting haemodynamics did not significantly predict survival. Multivariate analysis controlled for age revealed that mPAP increase during exercise (hazard ratio 1.097, 95% CI 1.002–1.200), mPAP increase per Watt (hazard ratio 8.131, 95% CI 2.209–29.928) and distensibility index α (hazard ratio 0.100, 95% CI 0.012–0.871) remained predictors of transplant free survival.

Discussion

In this study, we showed for the first time that SSc patients with PH_{ex} had worse transplant-free survival compared with SSc without pulmonary hypertension. The reduced transplant-free survival of SSc with PH_{ex} was similar to that of SSc patients with PH_{rest} (mPAP ⩾25 mmHg, PAWP ⩽15 mmHg). Transplant-free survival could be predicted by the maximal mPAP and increase in mPAP with exercise, but not by resting haemodynamics.

The diagnostic and prognostic value of pulmonary haemodynamics during exercise has been debated for a long time [12, 14, 23]. Recently, Hervé *et al.* [16] suggested that the combination of the two criteria, mPAP at maximal exercise >30 mmHg and TPVR >3 WU during exercise, identified patients who were shown to suffer from pulmonary vascular disease due to chronic thromboembolism or other aetiology according to subsequent clinical and/or histological evaluation. This approach including an exercise related, flow-dependent criterion retained sensitivity at 0.93 but improved specificity to 1.0 to diagnose pulmonary vascular disease compared to the maximal mPAP or TPVR during exercise. Expanding on these observations, we have recently shown that the pulmonary haemodynamic response to exercise predicts outcome in patients diagnosed with PAH or inoperable chronic thromboembolic pulmonary hypertension [19]. Few studies have investigated exercise haemodynamics by RHC in SSc patients [1, 12, 24, 25] and, to our knowledge, the



Patients at risk n

PH_{rest}	17	10	5	4	3	3	2	0	0
PH_{ex}	28	23	17	15	7	4	4	0	0
PH_{none}	27	23	18	15	12	7	4	1	1

FIGURE 2 Transplant-free survival by Kaplan–Meier method and number at risk of 72 patients according to their haemodynamic classification is shown. Patients were censored November 2015. PH_{rest}: resting precapillary pulmonary hypertension; PH_{ex}: exercise precapillary pulmonary hypertension; PH_{none}: patients without pulmonary hypertension.

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TABLE 4 Univariate Cox-proportional hazards analysis of transplantation or death for functional parameters and haemodynamics at rest and during exercise in 72 systemic sclerosis patients assessed during right heart catheterisation

	Hazard ratio (95% CI)	p-value
Age years	1.032 (0.977–1.090)	0.253
WHO–FC	3.423 (1.634–7.171)	0.001
6MWD m	0.997 (0.993–1.002)	0.241
NT-proBNP ng·L^{-1}	1.000 (1.000–1.001)	0.019
***D*LCO %**	0.966 (0.921–1.013)	0.151
FVC % predicted/*D*LCO % predicted	2.476 (1.015–6.041)	0.046
Tricuspid regurgitation velocity m·s^{-1}	1.378 (0.565–3.363)	0.481
Right atrium area cm^2	0.997 (0.858–1.159)	0.970
***S*aO$_2$ %**	0.788 (0.665–0.934)	0.006
***S*vO$_2$ %**	0.881 (0.807–0.963)	0.005
Resting haemodynamics by right heart catheterisation		
HR beats·min^{-1}	0.991 (0.938–1.048)	0.760
mBP mmHg	0.998 (0.955–1.042)	0.911
mPAP mmHg	1.029 (0.989–1.070)	0.152
PAWP mmHg	1.027 (0.823–1.280)	0.815
RAP mmHg	1.117 (0.921–1.355)	0.259
CO L·min^{-1}	0.891 (0.589–1.350)	0.587
Cardiac index L·min^{-1}·m^{-2}	0.686 (0.307–1.533)	0.358
PVR WU	1.118 (0.957–1.307)	0.161
Values obtained at maximal supine cycling exercise		
Maximal workload W	0.978 (0.930–1.028)	0.384
Maximal HR beats·min^{-1}	1.019 (0.981–1.059)	0.333
Maximal mBP mmHg	1.026 (0.984–1.069)	0.229
Maximal mPAP mmHg	1.039 (1.004–1.074)	0.028
Maximal PAWP mmHg	1.026 (0.910–1.160)	0.657
Maximal RAP mmHg	1.055 (0.943–1.180)	0.352
Maximal cardiac index L·min^{-1}·m^{-2}	0.778 (0.431–1.406)	0.406
Maximal CO L·min^{-1}	0.940 (0.740–1.254)	0.673
Maximal PVR WU	1.081 (0.977–1.196)	0.131
Maximal *S*vO$_2$ %	0.965 (0.900–1.034)	0.309
ΔmPAP/ΔCO mmHg·min·L^{-1}	1.015 (0.996–1.035)	0.127
Increase mPAP with exercise mmHg	1.103 (1.015–1.199)	0.021
Increase mPAP/power output mmHg·watt^{-1}	8.098 (2.408–27.236)	0.001
Distensibility index α %·mmHg^{-1}	0.1 (0.012–0.865)	0.036

WHO–FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: *N*-terminal pro-brain natriuretic peptide; *D*LCO: diffusing capacity of the lung for carbon monoxide; FVC: forced vital capacity of the lung; *S*aO$_2$: oxygen saturation (by radial artery blood gas analysis at rest and finger-tip or earlobe pulse-oximetry during exercise); *S*vO$_2$: mixed venous oxygen saturation; HR: heart rate; mBP: mean blood pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; RAP: right atrial pressure; TPG: transpulmonary gradient; CO: cardiac output; PVR: pulmonary vascular resistance.

current study is the first investigating the prognostic relevance of PHex in SSc patients diagnosed by the combined pressure and flow-related criteria.

In this cohort, SSc patients with PHex who did not fulfill criteria for pulmonary hypertension, had an mPAP and PVR at rest that was slightly higher compared with patients without pulmonary hypertension, thus their resting haemodynamics profile was intermediate between PHrest and PHnone (table 2). This intermediate haemodynamic profile of SSc patients with PHex persisted during exercise (table 2). These findings support the notion suggested previously [12, 26] that PHex may be a pathophysiological stage intermediate between normal haemodynamics and pulmonary vasculopathy with pulmonary hypertension at rest. In line with these assumptions, Condliffe *et al.* [1] found that 19% of patients with PHex progressed to PHrest after a mean time of 2 years and 108 days. We observed that patients with PHex were older, showed higher WHO–FC, higher serum levels of NT-proBNP and lower *S*pO$_2$ after 6MWD compared with SSc patients without pulmonary hypertension, all consistent with a more advanced clinical state. Hence, including exercise haemodynamics into the evaluation of SSc patients might help to identify those patients with pulmonary vascular disease who are at risk of developing PHrest and who might possibly benefit from

early therapy. In the current study, the PH_{rest} patients had relatively low PVR compared with the published cohort, potentially related to early pulmonary hypertension diagnosis resulting from the yearly screening programme for SSc patients with assessment of increasing dyspnoea and decreasing exercise capacity and D_{LCO} [27]. The comparably low percentage of postcapillary pulmonary hypertension in our cohort is due to our practice not to perform exercise RHC in patients with clinically clear resting postcapillary pulmonary hypertension. In our SSc cohort, the maximal workload achieved during exercise RHC was relatively low, especially in patients without pulmonary hypertension, potentially due to a combination of supine exercise with a 3-min step duration and/or lack of training in this chronically ill SSc population. Some patients without pulmonary hypertension revealed a comparatively high mPAP/cardiac output slope, mainly due to an inadequate increase in cardiac output despite a maximal mPAP well below 30 mmHg. During follow-up of these patients over 0.5–6.5 years, none developed PAH but three out of five developed left heart disease. PH_{rest} patients had higher PAWP at rest and PH_{rest} and PH_{ex} patients had higher PAWP at maximal exercise compared with patients without pulmonary hypertension. Although none of the PH_{ex} patients had a PAWP > 20 mmHg at maximal exercise, we cannot exclude a concurrent latent left heart disease with diastolic dysfunction in some of these elderly SSc patients.

Some studies reported that in patients with PAH associated with SSc, D_{LCO} was impaired, sometimes for many years prior to the development of PAH [3, 25, 28, 29]. Also an increase in FVC/D_{LCO} was found to be associated with increased risk for PAH [29] and was used as a variable in a two-step detection programme for PAH associated with SSc [30]. In our cohort, D_{LCO} and FVC/D_{LCO} ratio were similar between groups, most probably related to the fact that these parameters are part of our selection criteria to perform RHC in SSc patients and thus, our PH_{none} group might had a relatively low D_{LCO} due to selection bias. Another promising investigation to differentiate SSc patients with pulmonary vasculopathy from those not affected might be cardiopulmonary exercise testing [31], which was unfortunately not available in our cohort.

Survival

The diagnosis of PH_{ex} in SSc patients is relevant and associated with a worse transplant-free survival similar to that in PH_{rest}. This finding indicates that PH_{ex} is a sign of early, albeit prognostically relevant, pulmonary vascular disease in SSc patients known to be at risk of developing PAH. As this is not a prospective study, we do not have regular follow-up haemodynamics of all patients with PH_{ex} and thus do not know the percentage of patients who subsequently developed PAH. A hint towards a progressive nature of PH_{ex} from our study is the fact that four out of five patients with PH_{ex} died of progressive right heart failure. Whether early detection of pulmonary vascular disease in SSc patients and early treatment would increase transplant-free survival is still not clear. In the past years, prospective cohort studies using various approaches to the early detection of pulmonary vascular disease in SSc have been performed [9, 25, 30]. However, there is still no consensus about the best screening programmes, indicating the need for further studies.

It has been demonstrated that SSc patients with PAH, despite more favourable haemodynamics in RHC and comparable therapy, are more likely to die than patients with idiopathic PAH [8, 32–34]. Although survival improved in idiopathic PAH in the modern treatment era since 2002 when oral agents for PAH-specific treatment became available, it is controversial whether survival in SSc-associated PAH similarly improved [1, 33, 35]. The worse response to targeted therapy in SSc compared with idiopathic PAH may suggest that idiopathic and SSc-associated PAH have different pathophysiological mechanisms and/or that increased comorbidities in SSc contribute to an unfavourable therapeutic response [36, 37]. Whereas in idiopathic PAH a homogenous pattern of plexogenic arteriopathy is common, findings in SSc-PAH seem to be more heterogeneous with a remarkable proportion of fibrosis of pulmonary veins and venules, resembling a veno-occlusive disease. This may explain why SSc patients with PAH are less responsive to treatment compared with idiopathic PAH and have worse outcome [36]. In the present cohort, we found no difference in transplant-survival for PH_{ex} who received PAH-targeted therapy *versus* those who did not. As this is not a prospective randomised trial, it is not possible to conclude on the efficacy of PAH therapy in this subgroup.

In our cohort, survival was predicted by mPAP at maximal exercise and increase in mPAP during exercise in addition to baseline WHO–FC, resting S_{aO_2} and S_{vO_2}. Resting haemodynamics, on the other hand, did not predict survival emphasising the additional prognostic value of exercise compared with resting haemodynamics and other established clinical markers of disease severity in PAH.

Follow-up data of SSc patients who received PAH targeted therapy

All patients with PH_{rest} and 16 (57%) patients of PH_{ex} were treated with PAH-targeted therapy. During follow-up under therapy after 3, 12 and 24 months, 6MWD, serum NT-proBNP and haemodynamics by echocardiography did not change. However, compared with idiopathic PAH [10, 38], the role of these markers to predict disease severity and outcome in SSc is less clear, as they might be influenced by comorbidities [7, 32, 39, 40]. As treatment in the current study was not randomised, no firm conclusions

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on efficacy are possible. In addition, we did not do a comparative standardised follow-up assessment of functional class and 6MWD in PHex patients who did not receive PAH targeted therapy. Thus, randomised-controlled trials should elucidate the effectiveness of PAH targeted therapy in SSc patients with early pulmonary vascular disease manifesting as PHex.

Conclusions

This study indicates that PHex in SSc patients at risk for PAH represents an early form of pulmonary vascular disease. The fact that survival is reduced in SSc patients with PHex compared with PHnone supports the value of assessing pulmonary haemodynamics not only at rest, but also during exercise in these patients. The impaired outcome in SSc with PHex and the frequent disease progression to PHrest not only emphasise the need for development of early pulmonary hypertension detection strategies in SSc, but also suggest that research should be dedicated to answer the question whether initiation of early PAH-targeted medical therapy would improve outcome in this devastating disease.

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