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Reduced right ventricular output reserve in patients with systemic sclerosis and mildly elevated pulmonary arterial pressures

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Abstract

Objective:

The objective of this prospective study was to evaluate right ventricular function and pulmonary arterial compliance (PAC=stroke volume/pulse pressure) at rest and during exercise in patients with systemic sclerosis (SSc) with normal mean pulmonary artery pressures (mPAP) at rest, mildly elevated mPAP (mPAP 21-24mmHg) and manifest pulmonary hypertension (mPAP≥25mmHg).

Methods:

Patients with SSc (n=112) underwent clinical assessment and right heart catheterization at rest and during exercise and were divided into three groups according to their resting mPAP values: normal mPAP (≤20mmHg), mildly elevated mPAP (21-24mmHg) and pulmonary hypertension (PH, mPAP ≥25mmHg). Results were compared between groups by ANOVA followed by post-hoc student's t-test.

Results:

Compared to patients with normal mPAP, patients with mildly elevated mPAP showed lower 6-minute-walking distance (6MWD; $p<0.008$), lower cardiac index (CI) ($p=0.027$) and higher PVR ($p=0.0002$) during exercise and lower PAC at rest ($p=0.016$) and different stages of exercise (25 Watts $p=0.033$, 75 Watts $p=0.024$).

Conclusion:

The results of this study suggest that impaired 6MWD in SSc-patients with mildly elevated mPAP might be caused by reduced PAC during exercise and reduced RV output reserve, presumably due to impaired coupling between the right ventricle and the pulmonary vasculature. These findings give further evidence for the clinical relevance of mildly elevated mPAP in patients with SSc.

Introduction

The natural course of systemic sclerosis (SSc) is often complicated by the occurrence of pulmonary arterial hypertension (PAH)(1, 2). Patients with SSc-associated pulmonary arterial hypertension (SSc-PAH) have a lower survival rate compared to patients with idiopathic PAH (IPAH)(3, 4). The current haemodynamic definition of PAH is a resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg with elevated pulmonary vascular resistance (PVR) measured invasively by right heart catheter (RHC)(7, 8). A post-hoc analysis of the DETECT study on SSc-patients demonstrated that mildly elevated mPAP levels between 21 and 24 mmHg may represent an intermediate stage between normal mean pulmonary artery pressures (<21mmHg) at rest and manifest PH (9). Previous studies have shown that patients with mildly elevated mPAP have reduced exercise capacity, higher World Health Organisation (WHO) functional class (FC)(6, 10), a high risk of developing manifest PH (11), and an impaired prognosis (1). However, the pathophysiological mechanisms underlying exercise intolerance in mPAP 21-24mmHg remain incompletely characterized.

In the current study we sought to evaluate the response of the right ventricle (RV) and pulmonary vasculature to exercise in three different groups of SSc-patients: mPAP <21mmHg (normal resting mPAP), mPAP 21-24mmHg (formerly borderline-mPAP) and mPAP ≥ 25mmHg (manifest pulmonary hypertension). The question was whether these three groups show significant differences in right ventricular output reserve measured by an increase in cardiac index (CI) under exercise and pulmonary arterial compliance (PAC) measured by Swan-Ganz right heart catheter (RHC) in routine clinical practice. RV output reserve is an emerging parameter which has shown to be of prognostic importance in patients with PH(15, 16).For estimation of PAC (or capacitance) the measurement of stroke volume/pulse pressure (cardiac output/heart rate)/(systolicPAP-diastolicPAP) by RHC has been shown to be the most simple and practical method(17, 18).Furthermore RV output reserve and PAC may add crucial information to detect pulmonary vascular disease in this at-risk-population at an early stage (13, 14), which may also add to defining an indication for early targeted treatment**.**

Methods

Study population and design

Patients affected by diffuse cutaneous SSc (dc-SSc) and limited cutaneous SSc (lc-SSc) referred to our centre for the purpose of PH screening were prospectively and consecutively enrolled in this study between October 2012 and August 2016. The referring specialists were rheumatologists, cardiologists, pulmonologists and general practitioners. Definite diagnosis of SSc was confirmed by experienced rheumatologists (HL, NB, CF) according to the standard criteria of the American College of Rheumatology (19). Exclusion criteria were: inability to perform exercise RHC, manifest PH confirmed by RHC prior to enrolment, receiving PAH therapy, renal insufficiency, systemic arterial hypertension with pressure values >180/95 mmHg at rest or >230/120 mmHg during exercise despite optimized medical treatment, previous evidence of clinically relevant left heart or lung disease or pregnancy.

All patients who were referred to our centre who did not fulfil exclusion criteria were entered into the study even if baseline Echo did not suggest PH

All patients underwent a detailed clinical work-up including medical history, physical examination, electrocardiogram, 2-Dimensional-echocardiography at rest, lung function test, arterial blood gases, chest X-ray, functional class (FC) assessment, 6-minute walking distance (6MWD) under standardized conditions (20), laboratory testing including N-terminal pro brain natriuretic peptide (NTpro-BNP) levels, and RHC at rest and during exercise. 12-lead electrocardiogram was performed in all patients (Hellige EK 512 P, Hellige, Germany). High resolution computed tomography (CT), ventilation/perfusion SPECT and CT angiography of the lungs were performed in all patients to diagnose/exclude patients with suspected chronic thromboembolic PH, interstitial lung disease, or other respiratory diseases. Left heart catheterization was performed in all patients with suspected left heart disease. Manifest PH/PAH was diagnosed according to the current ERS/ESC-guidelines (8).

Definition of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH)

PH and PAH were defined according to current ESC/ERS Guidelines (41). The haemodynamic definition for PH is mPAP ≥25mmHg, the definition for PAH (group 1 according to WHO classification) is ≥25mmHg and pulmonary arterial wedge pressure (PAWP) ≤15mmHg.

Right heart catheter (RHC)

SSc patients were consecutively referred to RHC in in order to screen this at-risk-population for manifest PH. Patients were examined on a variable load supine bicycle ergometer (model 8420; KHL Corp., Kirkland, Washington) by experienced investigators (CN, BE). The examination at rest was performed as previously described (1) in a supine position using the transjugular access with an 8F introducer set (MXI100, MEDEX, Smiths Group PLC, UK). Catheterization was done by triple-lumen 7F-Swan-Ganz thermodilution catheters by Edwards Lifesciences (REF:131F7, Edwards Lifesciences LLC, Irvine, CA, USA). After the hemodynamic measurement at rest, the supine position was changed to a 45° position. The zero reference point for pressure recordings was set at midchest at the insertion of the 4th rib to the sternum in line with current recommendations(21) on the left atrial level. Zero levelling at 45°position was performed at the intersection of the frontal plane at the midthoracic level, the transverse plane at the level of 4th anterior intercostal space and the midsagittal plane on the left atrial level(22). The pulmonary vascular pressures (mPAP, PAWP) were averaged throughout three respiratory cycles. Cardiac output (CO) was measured at least in triplicate at rest and in duplicate at the end of each workload step during exercise by thermodilution with a variation of <10% between the measured values. Exercise testing started at 25 W and was increased every 2 min for 25 W until symptom-limited exercise capacity was reached. The pulmonary vascular pressures (mPAP, PAWP), CO, heart rate and systemic blood pressure were measured at the end of each workload step(22) in line with current recommendations.

Transpulmonary pressure gradient (TPG) was defined as the difference between mPAP and PAWP. PAC was calculated according the formula PAC=stroke volume/ pulse pressure; (CO/Heart rate)/(sPAP-dPAP). Right ventricular output reserve was defined and measured by the increase in cardiac index (CI) during incrementally increased exercise on the variable load supine bicycle ergometer compared to CI at rest. All examinations and measurements were performed by the same experienced team (CN, BE, SH). There were no complications.

Transthoracic Doppler echocardiography at rest

A complete left- and right-sided echocardiographic examination was done as described previously (14). Two-dimensional and colour-flow guided continuous-wave-Doppler-echocardiographic recordings at rest were obtained by experienced cardiac sonographers (CN, BE, SH, EG) using 3.6-4 MHz Duplex probes and conventional equipment (Vivid 7, GE Healthcare, Milwaukee, Wisconsin) at rest as described before (14). Pulmonary arterial systolic pressure (PASP) was estimated from peak tricuspid regurgitation jet velocities according to the equation: PASP= 4 $(V)^2$ + right atrial pressure, where V is the peak velocity (in m/s) of tricuspid regurgitation velocity (23). For all calculations the mean value of at least 3 tricuspid regurgitation velocity measurements was used. Right atrial pressure was estimated from characteristics of the inferior vena cava (24). If it was <20mm in diameter and decreased during inspiration 5 mmHg were added, ≥20 mm 10mmHg were added, respectively.

Ethics statement

This study was conducted in accordance with Good Clinical Practice (GCP) and the current version of the revised Declaration of Helsinki (WMA Declaration of Helsinki). The ethics committee of the University of Heidelberg approved the study (Internal Ethics-Nr. S-360/2009). The trial was registered in Clinicaltrials.gov (NCT01387035). Written informed consent was obtained from each patient prior to enrolment.

Statistical Methods

Statistical analyses were conducted by two statisticians (CF, NB). Data are described as mean ± standard deviation or number and %, respectively. Patients were divided into three groups according to their resting mPAP values: normal mPAP (mPAP ≤20 mmHg), mildly elevated PAP (21-24 mmHg) and manifest PH (mPAP≥ 25 mmHg) (Figure 1). At rest, the three groups (normal mPAP, mildly elevated PAP and manifest PH) were compared using analysis of variance (ANOVA) for quantitative variables and Chi square tests or exact Fisher Tests for categorical variables. The comparison of variables at rest and various levels of exercise or maximum level of exercise between the three groups were performed by ANOVA and mixed model ANOVA, respectively. If the ANOVA detected a significant difference, results were followed by post-hoc tests between normal and mildly elevated mPAP. Post-hoc analyses were conducted with student's t-tests. All tests were two-sided and a p-value of 0.05 was considered statistically significant. For post-hoc tests, statistical significance remained when p-values were <0.016, <0.025 and <0.05 for the first, second and third p-value when ordered from lowest to highest (Bonferroni-Holm correction).

Correlation of PAC at rest with 6MWD, Δ CO and Δ CI was performed with Pearson correlation analysis.

All analyses have been performed using IBM SPSS 23 (SPSS Statistics V23, IBM Corporation, Somers, New York).

Results

Clinical Characteristics

We prospectively included 116 patients diagnosed with SSc. Four patients were excluded due to inability to perform RHC. One patient refused RHC assessment due to painful skin. Three patients were not able to perform exercise RHC due to knee or hip problems. There

were no complications. Thus, the final study group consisted of 112 patients with SSc (88 females, mean age 57±13 years; 76 (67.9%) with dc-SSc and 36 (32.1%) with lc-SSc (CREST Syndrome) (Table 1). According to RHC measurements at rest, 72 patients presented with normal mPAP ≤20 mmHg (64.3%), 14 with mildly elevated mPAP (21-24mmHg; 12.5%) and 26 with manifest PH (mPAP≥ 25 mmHg; 23.2%, Figure 1).

The patients with PH had been newly diagnosed during the study. Most of them had been diagnosed at a relatively early stage of disease with an mPAP of 32.5±7.2mmHg, a mean PVR of 326.2±188.3dynes·sec·cm^{-5}, and normal RV function at rest but with impaired WHO functional class and exercise capacity (Table 1). Out of the 26 PH-patients, 10 had PAH, 8 PH due to left heart disease, and 8 PH due to lung disease. Out of 14 patients with mildly elevated mPAP, two had concomitant coronary artery disease and five had concomitant interstitial lung disease.

Comparison of clinical parameters

The three groups (normal mPAP, mildly elevated mPAP, manifest PH) differed in age, with manifest PH showing the highest mean age (normal mPAP 54.1±12.9 years, mildly elevated mPAP 58.1±11.0 years, manifest PH 66.7±9.3 years; ANOVA p<0.0001; table 1). The Modified Rodnan Skin Score (MRSS) also differed between groups with normal mPAP 12.6±7.5, mildly elevated mPAP 20.3±11.2 and manifest PH 18.9±11.1 (ANOVA p=0.019; table 1). There were no significant differences between patients with normal and mildly elevated mPAP with regards to sex, body size, duration of SSc and FC (Table 1). A comparable prevalence of coronary artery disease (CAD), mild SSc associated interstitial lung disease and arterial hypertension was found among the three different groups.

Although patients with mildly elevated mPAP had higher values of resting systolic blood pressure than those with normal mPAP (138.6±16.9mmHg vs. 120.1±15.1mmHg, p=0.001), the systolic blood pressures during maximum workload did not significantly differ to patients with normal mPAP at rest (156.9±22.8mmHg vs. 167.6±26.8mmHg, p>0.05; table 1). Furthermore, PAWP during exercise did not significantly differ between groups.

Exercise capacity

The mean 6MWD significantly differed (ANOVA p<0.0001) between the three groups with lowest walking distance in the manifest PH group (342±87 meters), followed by patients with mildly elevated mPAP (396±87 meters) and highest walking distance in the normal mPAP group (474±79 meters; table 1). Patients with mildly elevated mPAP had a significantly lower mean 6MWD compared to the group with normal haemodynamics (p=0.008; table 1).

The difference in exercise capacity could also be seen in a different peak workload (ANOVA p<0.001) with highest peak workload in patients with normal mPAP (76.7±21.9 Watts), and lowest peak workload in patients with manifest PH (51.9±19.9 Watts). Peak workload in patients with mildly elevated mPAP was lower than in patients with normal mPAP (mildly elevated mPAP 62.5±25.5 Watts; p=0.033). Patients with mildly elevated mPAP did not significantly differ from manifest PH in peak workload.

Echocardiography

The echo measurements showed no significant differences between patients with normal mPAP and mildly elevated mPAP regarding the size of the right atrium (RA) and the right ventricle (RV) as well as systolic function measured by tricuspid annular plane systolic excursion (TAPSE) and estimated pulmonary arterial systolic pressure (PASP) assessed by transthoracic Doppler echocardiography (TDE) at rest. As expected patients with manifest PH revealed larger RA (15.5±5.3cm^2 vs. 11.6±3.2cm^2, p=0.001) and RV area (17.9±4.2cm^2 vs. 14.8±3.8cm^2, p=0.001) as well as a thicker RV free wall (7.5±1.3mm vs. 6.5±1.2mm, p=0.004) than patients with normal haemodynamics (table 1). Patients with mildly elevated mPAP at rest significantly differed from patients with manifest PH in RA area (p=0.004), RV area (p=0.003), sPAP (p<0.001) and RV free wall (p=0.016; table 1).

Pulmonary haemodynamics at rest

Patients with mildly elevated mPAP showed significantly higher mean pulmonary vascular resistance (PVR) at rest when compared with patients in the normal mPAP group (179±32

vs. 117±45 dynes·sec·cm^{-5}; p=0.001) (Table 2) and higher transpulmonary pressure gradient (TPG) (12.7±3 vs. 7.5±2.6 mmHg, p<0.0001; table 2). Values for PVR and TPG were significantly lower than in patients with manifest PH (p=0.001 and p<0.0001, table 2).

Mean PAWP were within normal range in patients with normal mPAP, mildly elevated mPAP and manifest PH (Table 2). No differences were found regarding right atrial pressures (RAP), as well as RV function at rest (CO and CI at rest, ns) among all groups (table 2).

Pulmonary haemodynamics during exercise

Patients with mildly elevated mPAP reached significantly higher mean (mPAP) and systolic pulmonary pressures (sPAP) at peak workload compared to patients with normal mPAP at rest (37.4±6.3mmHg vs. 31.7±7.5mmHg, p<0.0001). Patients with mildly elevated mPAP had a significantly lower increase in CO and cardiac index (CI) during exercise than patients with normal mPAP (peak CI: 5.4±0.9 vs. 6.3±1.8 l/min·m^{-2}, p=0.027; ΔCI 2.1±1.2 vs. 3.3±1.5 l/min·m^{-2}, p=0.006) (table 2) and did not significantly differ from patients with manifest PH.

CI increases during exercise showed an almost congruent course in patients with mildly elevated mPAP and manifest PH up to the 50 Watts level (Figure 3). At 75 Watts, patients with mildly elevated mPAP patients showed a lower mean CI increase than patients with manifest PH (ANOVA three groups p=0.009; normal mPAP vs. mildly elevated mPAP p=0.005). Two patients with mildly elevated mPAP dropped their CI during exercise, one at 25 and one at 50 Watts.

Patients with mildly elevated mPAP had a significantly higher TPG than patients with normal mPAP for values at rest, 25 Watts (both p<0.001), 75 Watts (p=0.008) and showed a trend at 50 Watts (p=0.059). The slope of TPG-increase during exercise was similar in patients with mildly elevated mPAP and normal mPAP.

PAC significantly differed between the three groups at rest and for each workload (each p≤0.01). Patients with mildly elevated mPAP had a significantly lower PAC than patients with normal mPAP at rest (p=0.016), as well as at 25 (p=0.033) and 75 (p=0.024) Watts (Figure

4). PAC at rest significantly correlated with 6MWD (R=0.448, p<0.001), Δ CO (R=0.227, p=0.018) and correlated in trend with Δ CI (R=0.178, p=0.064).

Discussion

To the best of our knowledge, this is the first prospective study assessing RV output reserve and PAC in SSc-patients with mildly elevated mPAP in comparison to SSc patients with normal mPAP at rest and SSc-patients with manifest PH. The study showed that SSc-patients with mildly elevated mPAP had normal CI-values at rest but a reduced RV output reserve (defined as reduced CI during exercise) and a reduced PAC compared to SSc-patients with normal mPAP at rest. Furthermore, the study revealed that SSc-patients with mildly elevated mPAP had higher PVR and TPG values than patients with normal mPAP. The impairment in RV function and pulmonary haemodynamics in patients with mildly elevated mPAP was associated with lower 6MWD and reduced peak exercise capacity compared to SSc patients with normal resting haemodynamics.

Reduced RV output reserve in SSc-patients with mildly elevated mPAP

Mean RV CI at rest was normal and did not differ between SSc-patients with normal or mildly elevated mPAP as previously described(6, 9, 25). Even right heart size (mean right atrial and ventricular areas) measured by echocardiography were comparable between both groups. Thus, reduced RV output reserve, reduced PAC and higher PVR and TPG were the only hemodynamic parameters characterizing patients with mildly elevated mPAP and might be the pathophysiological underpinning of symptoms and reduced 6MWD/exercise capacity in these patients. These data suggest that exercise haemodynamics might be more sensitive to early RV dysfunction and vascular remodeling than resting haemodynamics.

RV output reserve and contractile reserve have been previously assessed in PAH patients using different methods and surrogate parameters: by invasive single-beat pressure-volume loop analysis(26-28), by stress Doppler-echocardiography (SDE) assessing the capability of patients to increase right ventricular systolic pressure during low-level exercise (14) and by

echocardiographic strain during SDE (29). Although invasive single-beat pressure-volume loop analysis (30) is most likely the most sophisticated method to evaluate load-independent RV contractile reserve, its application can be dangerous for patients (stiff catheters), is too costly and complex for routine clinical practice and needs special equipment like conductance catheters with special software for online pressure-volume signals (30, 31) and transit-time ultrasonic flow probes (26). Therefore, the assessment of CI increase during exercise by RHC using Swan-Ganz catheters has been used in PAH patients before (15, 16) and has been performed in this study. It seems to be a simple and useful method to measure RV output reserve.

Reduced PAC in mildly elevated mPAP might indicate early vascular remodelling

Whereas RV function was impaired during exercise only, PAC was already significantly reduced at rest and during all exercise levels in patients with mildly elevated mPAP and PH-patients compared to patients with normal mPAP (Figure 4). Decreased PAC has been described in patients with idiopathic PAH (18) and was correlated with PH severity (32). In the present study, PAC was calculated from RHC data and it has been shown that PAC may detect early vascular disease in patients at risk for PAH. This finding is in line with the elevated PVR and TPG in SSc patients with mildly elevated mPAP, which has already been found in a retrospective study of Kovacs et al 2014(6)**.**

A reduced PAC increases RV pulsatile workload (33) and can lead to RV dysfunction and failure. (34, 35)**.** PAC in PAH patients was a stronger predictor of prognosis and response to therapy than PVR alone (36-39).

Myocardial function in SSc

RV-PA uncoupling requires pulmonary vascular disease, reduced RV output reserve or both. SSc patients show myocardial involvement even in the absence of PH. Hsu et al showed that patients with SSc who do not yet have resting PAH also exhibit abnormal sarcomere function due to reduced maximal calcium-activated tension and abnormal increase in calcium

sensitivity (42). This depressed RV output reserve was also observed in manifest SSc-PAH compared to idiopathic PAH (43,28).

Beside a possible early pulmonary vascular disease indicated by reduced PAC, patients with mildly elevated pulmonary arterial pressures in SSc might also be affected by impaired myocardial contractility and might therefore be more affected in their exercise capacity, symptom load and quality of life.

Overlap of mPAP 21-24mmHg and exercise induced PH

A resting mPAP 21-24mmHg is above the upper limit of normal but below the criteria of manifest PH. Exercise PH is defined as mPAP >30mmHg and total pulmonary resistance (TPR) >3 WU (44). Lau et al showed a high overlap of mPAP 21-24mmHg with exercise PH with 86% in an at-risk population that was nearly twice as high as the group with mPAP <21mmHg (45). This overlapping population was associated with worse functional capacity (45), increased progression to resting PH (11) and survival (46, 6). Oliveira et al found that exercise PH is most frequently found in mPAP 21-24mmHg and is reducing exercise capacity similar to resting PH (47). Our group with mPAP <21mmHg at rest fulfilled the criteria for exercise PH in 22 of 72 patients (30.6%) vs. 11 of 14 patients (78.6%) in the group with mPAP 21-24mmHg and is in line with the observation of Oliveira et al 2017. However, in our study, regression and correlation analysis revealed a significant correlation of PAC at rest with 6MWD ($R=0.448$, $p<0.001$), Δ cardiac output ($R=0.227$, $p=0.018$) and a trend with Δ cardiac index ($R=0.178$, $p=0.064$) (Figure 2). This supports the hypothesis that PAC and RV output reserve play another important role apart from exercise induced PH in exercise limitation of SSc patients with mPAP 21-24mmHg.

Early treatment as future strategy

The described changes in RV function during exercise and pulmonary haemodynamics at rest and during exercise in patients with mildly elevated mPAP raise the question whether targeted PAH therapy could enhance these impairments and would be justified in these

patients. In our study, those patients with reduced PAC may already be manifesting increased resting PVR, which supports the idea of an early targeted treatment. In a pilot study, bosentan was safe and effective in patients with SSc and mildly elevated mPAP (40). Larger clinical trials with relevant outcome measures are needed to define the appropriate indication, safety and tolerability of early treatment.

Study Limitations

The study results may be influenced by the rather small sample size. As not all patients reached high workloads, we only reported values up to 75 Watts. Furthermore, the presentation of CI and TPG for each workload is an approximation and may be distorted, as different peak workload levels were reached.

The method we used to calculate PAC may overestimate compliance as it does not account for blood flow from the pulmonary circulation into the capillary bed during systole (17). Thus, the true reduction of PAC in patients with mildly elevated mPAP may be even higher.

Patients with mildly elevated mPAP had higher values of resting systolic blood pressure than those with normal mPAP. However, the systolic blood pressure at peak workload was not significantly higher than that of the normal mPAP group. Furthermore, PAWP during exercise did not significantly differ between groups. This indicates that systemic blood pressures were no explanation for the reduced CI increase during exercise in patients with mildly elevated mPAP.

Data from 2D echo under exercise would have been helpful for interpretation of the results but were not part of the initial protocol.

Conclusion

The results of this study suggest that impaired 6MWD and exercise capacity in SSc-patients with mildly elevated mPAP (and normal RV function at rest) might be caused by reduced PAC and reduced RV output reserve (reduced RV output during exercise). These findings

give further evidence for mildly elevated mPAP reflecting an early stage of pulmonary vascular disease and RV dysfunction. Screening of SSc-patients using right heart catheter at rest and during exercise may lead to an identification of early pulmonary vascular disease. Further studies are needed to evaluate if it is useful to start PAH targeted medication in SSc patients with mildly elevated mPAP.

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Figure legends

Figure 1

The study flow-chart describes the study cohort, reasons for exclusion and group allocations.

Figure 2

Pearson's correlation analysis of PAC vs. 6MWD show a significant correlation of PAC at rest with 6MWD. mPAP-values $\leq$ 20mmHg are coded as green dots, mPAP 21-24mmHg are coded as orange triangles and mPAP $\geq$ 25mmHg are coded as red squares.

Figure 3

The slope of CI increase during exercise showed similar values for patients with mildly elevated mPAP and manifest PH. For each stage, the p-value of the respective ANOVA

between the three groups is shown. At 75 Watts, mildly elevated mPAP patients had a significantly smaller increase in CI than patients with normal mPAP (t-test p=0.005).

Figure 4

PAC significantly differed between groups for each workload level (ANOVA each p≤0.01). Patients with mildly elevated mPAP had a significantly lower PAC than patients with normal mPAP both at rest (p=0.016), and during exercise at 25 (p=0.033) and 75 (p=0.024) Watts.

Table 1. Clinical characteristics of the overall study population and the three hemodynamic groups

	All patients (n=112)	(n)	normal mPAP (n=72)	(n)	Mildly elevated mPAP (n=14)	(n)	manifest PH (n=26)	(n)	p value *among groups* (ANOVA)	p value *normal vs. mildly elevated mPAP* (t-test)	p value *mildly elevated mPAP vs. manifest* (t-test)	p value *normal vs. manifest* (t-test)
Females, n (%)	88 (78.6)		55 (76.4)		12 (85.7)		21 (80.8)		ns	nt	nt	nt
Age, years	57.5 ± 13.0		54.1 ± 12.9		58.1 ± 11.0		66.7 ± 9.3		<0.0001	ns	0.014	<0.0001
Height, cm	165.4 ± 8.3		166.8 ± 7.7		163.5 ± 9.0		162.7 ± 8.9		ns	nt	nt	nt
Weight, kg	70.2 ± 15.1		71.8 ± 16.8		69.6 ± 12.0		66.2 ± 10.7		ns	nt	nt	nt
SBP, mmHg	124.6 ± 18.6		120.1 ± 15.1		138.6 ± 16.9		129.5 ± 23.4		0.001	0.001	ns	0.063
DBP, mmHg	78.3 ± 11.1		77.1 ± 9.6		80.5 ± 13.6		80.3 ± 13.4		ns	nt	nt	nt
6MWD, m	436 ± 98	*(105)*	474 ± 79	*(69)*	396 ± 87	*(13)*	342 ± 87	*(23)*	<0.0001	0.008	ns	<0.0001
NT-proBNP, ng/ml	385 ± 580		201 ± 239		444 ± 677		977 ± 897		<0.001	ns	ns	0.005
SSc characteristics												
Type of SSc									ns	nt	nt	nt
dc-SSc, n (%)	76 (67.9)		46 (63.9)		11 (78.6)		15 (57.7)					
lc-SSc (CREST), n (%)	36 (32.1)		26 (36.1)		3 (21.4)		11 (42.3)					
Disease duration, years	10.1 ± 9.1		8.6 ± 8.7		14.3 ± 9.8		11.7 ± 9.3		ns	nt	nt	nt
Digital ulcers, n (%)	31 (27.7)		19 (26.4)		2 (14.3)		10 (38.5)		ns	nt	nt	nt
MRSS	14.8 ± 9.2	*(70)*	12.6 ± 7.5	*(47)*	20.3 ± 11.2	*(3)*	18.9 ± 11.1	*(20)*	0.019	ns	ns	0.029
Concomitant diseases												
Mild SSc ILD, n (%)	31 (27.7)		17 (23.6)		5 (35.7)		9 (34.6)		ns[#]	nt[#]	nt[#]	ns[#]
CAD, n (%)	13 (11.6)		7 (9.7)		2 (14.3)		4 (15.4)		ns[#]	nt[#]	nt[#]	ns[#]
Arterial Hypertension, n (%)	34 (30.4)		16 (22.2)		5 (35.7)		13 (50.0)		<0.028[#]	ns[#]	ns[#]	<0.008[#]
Lung function												
VC max (%)	93.9 ± 23.2		98.3 ± 20.6		77.3 ± 18.1		90.4 ± 28.1		0.007	0.001	ns	ns
FEV1 (%)	91.0 ± 23.3		96.7 ± 20.4		71.7 ± 18.5		85.3 ± 26.7		<0.001	<0.001	ns	0.028
TLC (%)	93 ± 22		96 ± 22		85 ± 20		88 ± 25		ns	nt	nt	nt
Echocardiography												
RV free wall thickness, mm	6.7 ± 1.2	*(90)*	6.5 ± 1.2	*(61)*	6.5 ± 0.7	*(11)*	7.5 ± 1.3	*(18)*	0.007	ns	0.016	0.007
TAPSE, mm	23.6 ± 4.5		24.1 ± 3.8		24.1 ± 6.7		21.8 ± 4.7		ns	nt	nt	ns
RA area, cm²	12.5 ± 4.1	*(111)*	11.6 ± 3.2	*(71)*	11.0 ± 2.3	*(14)*	15.5 ± 5.3	*(26)*	<0.0001	ns	0.004	<0.0001
RV area, cm²	15.4 ± 4.1		14.8 ± 3.8		13.8 ± 3.2		17.9 ± 4.2		0.001	ns	0.003	0.001
estimated sPAP* , mmHg	32.0 ± 14.5	*(111)*	26.1 ± 7.2	*(71)*	27.9 ± 4.6	*(14)*	50.2 ± 17.9	*(26)*	<0.0001	ns	<0.0001	<0.0001
Pericardial Effusion, n (%)	5 (4.5)		1 (1.4)		2 (14.3)		2 (2.7)		ns	nt	nt	ns
WHO-FC												
I, n (%)	19 (17.0)		18 (25.0)		1 (7.1)		0 (0)		<0.0001[#]	ns[#]	0.030[#]	<0.0001[#]
II, n (%)	62 (55.3)		45 (62.5)		9 (64.3)		8 (30.8)					
III, n (%)	31 (27.7)		9 (12.5)		4 (28.6)		18 (69.2)					
IV, n (%)	0 (0)		0 (0)		0 (0)		0 (0)					

PAP pulmonary arterial pressure; mildly elevated mPAP: mean pulmonary arterial pressure 21-24mmHg; PH: pulmonary Hypertension; 6MWD: 6 minute walking distance; SBP: systolic blood pressure; DBP: diastolic blood pressure; SSc: systemic sclerosis; dc: diffuse cutaneous; lc: limited cutaneous; MRSS: modified Rodnan Skin Score; SSc-ILD: Systemic sclerosis associated interstitial lung disease; CAD: Coronary Artery Disease; RV: Right Ventricle; TAPSE: tricuspid annular plane systolic excursion; RA: Right Atrium; sPAP: systolic pulmonary arterial pressure; WHO-FC: World Health Organization Functional Class; ns: not significant at the 0.05 level; nt: not tested; [#]tested with chi square test; *measured with transthoracic echocardiography. Values derive from the full sample of each group, unless otherwise indicated.

Table 2. Resting and Exercise Haemodynamics

	normal mPAP (n=72)	Mildly elevated mPAP (n=14)	manifest PH (n=26)	p value *among groups* (ANOVA)	p value *normal vs. mildly elevated mPAP* (t-test)	p-value *mildly elevated mPAP vs. manifest (t-test)*	p-value *normal vs. manifest (t-test)*
Rest							
RAP, *mmHg*	4.1 ± 2.8	4.5 ± 3.0	6.8 ± 4.5	0.003	ns	0.096	0.008
sPAP, *mmHg*	24.3 ± 4.6	33.5 ± 4.0	54.4 ± 15.1	<0.0001	<0.0001	<0.0001	<0.0001
dPAP, *mmHg*	9.6 ± 2.5	12.8 ± 2.1	20.9 ± 5.7	<0.0001	<0.0001	<0.0001	<0.0001
mPAP, *mmHg*	14.9 ± 3.0	22.0 ± 1.0	32.5 ± 7.2	<0.0001	<0.0001	<0.0001	<0.0001
PAWP, *mmHg*	7.5 ± 3.0	9.3 ± 2.8	12.8 ± 5.7	<0.0001	0.039	0.013	<0.0001
TPG, *mmHg*	7.5 ± 2.6	12.7 ± 3.0	19.7 ± 9.7	<0.0001	<0.0001	0.001	<0.0001
CO, *l/min.*	5.3 ± 1.2	5.7 ± 1.0	5.1 ± 1.0	ns	nt	nt	nt
CI, *l/min·m^{-2}*	3.0 ± 0.6	3.3 ± 0.6	3.0 ± 0.5	ns	nt	nt	nt
PVR, *dynes·sec·cm^{-5}*	117 ± 45	179 ± 32	326 ± 188	<0.0001	0.001	<0.0001	<0.0001
Peak workload							
sPAP, *mmHg*	48.8 ± 12.6	57.6 ± 10.2	84.4 ± 20.6	<0.0001	0.006	<0.0001	<0.0001
dPAP, *mmHg*	21.7 ± 6.3	24.1 ± 5.7	30.4 ± 7.5	<0.0001	ns	0.098	<0.0001
mPAP, *mmHg*	31.7 ± 7.5	37.4 ± 6.3	49.2 ± 10.0	<0.0001	<0.0001	<0.0001	<0.0001
PAWP, *mmHg*	13.2 ± 6.7	13.4 ± 6.8	14.4 ± 7.0	ns	nt	nt	nt
TPG, mmHg	18.4 ± 7.4	24.7 ± 7.4	34.8 ± 13.1	<0.0001	0.034	0.009	<0.0001
CO, *l/min*	11.1 ± 3.0	9.2 ± 2.3	8.5 ± 2.8	<0.0001	0.04	ns	<0.0001
CI, *l/min·m^{-2}*	6.3 ± 1.8	5.4 ± 0.9	4.9 ± 1.5	0.001	0.027	ns	0.001
PVR, *dynes·sec·cm^{-5}*	140 ± 64	215 ± 77	377 ± 212	<0.0001	0.0002	0.001	<0.0001
SBP, *mmHg*	168 ± 27	157 ± 23	173 ± 22	ns	nt	nt	nt
DBP, *mmHg*	90.7 ± 12.0	88.9 ± 14.1	93.9 ± 15.5	ns	nt	nt	nt
Workload (Watt)	76.7 ± 21.9	62.5 ± 25.5	51.9 ± 19.9	<0.0001	0.033	ns	<0.0001
Δ sPAP *(mmHg)*	24.2 ± 11.0	23.6 ± 8.06	29.0 ± 12.4	ns	nt	nt	nt
Δ dPAP *(mmHg)*	12.1 ± 6.3	11.2 ± 5.95	9.5 ± 5.5	ns	nt	nt	nt
Δ mPAP *(mmHg)*	16.7 ± 7.1	15.4 ± 6.11	16.7 ± 7.1	ns	nt	nt	nt
Δ PAWP *(mmHg)*	5.8 ± 6.8	4.1 ± 6.42	1.6 ± 5.0	0.02	ns	ns	0.002
Δ TPG (mmHg)	18.4 ± 7.4	24.1 ± 7.38	34.8 ± 13.1	ns	nt	nt	nt
Δ CO *(l/min)*	5.8 ± 2.6	3.5 ± 2.50	3.3 ± 2.2	<0.0001	0.003	ns	<0.0001
Δ CI (l/min·m^{-2})	3.3 ± 1.5	2.1 ± 1.18	1.9 ± 1.2	<0.0001	0.006	ns	<0.0001
Δ PVR *(dynes·sec·cm^{-5})*	24 ± 68	36 ± 92	51 ± 110	ns	nt	nt	nt
Δ SBP *(mmHg)*	47.4 ± 27.3	19.2 ± 22.1	43.5 ± 28.1	0.004	0.001	0.01	ns
Δ DBP *(mmHg)*	13.3 ± 15.1	6.8 ± 16.7	13.7 ± 15.6	ns	nt	nt	nt
Δ HR *(bpm)*	48.7 ± 20.7	41.9 ± 12.7	45.3 ± 25.1	ns	nt	nt	nt

PAP pulmonary arterial pressure; mildly elevated mPAP: mean pulmonary arterial pressure 21-24mmHg; PH: pulmonary Hypertension; RAP: right atrial pressure; sPAP: systolic pulmonary arterial pressure; dPAP: diastolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; TPG: transpulmonary pressure gradient; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate
ns: not significant at the 0.05 level; nt: not tested *measured with transthoracic echocardiography

Figure 1: study flow-chart

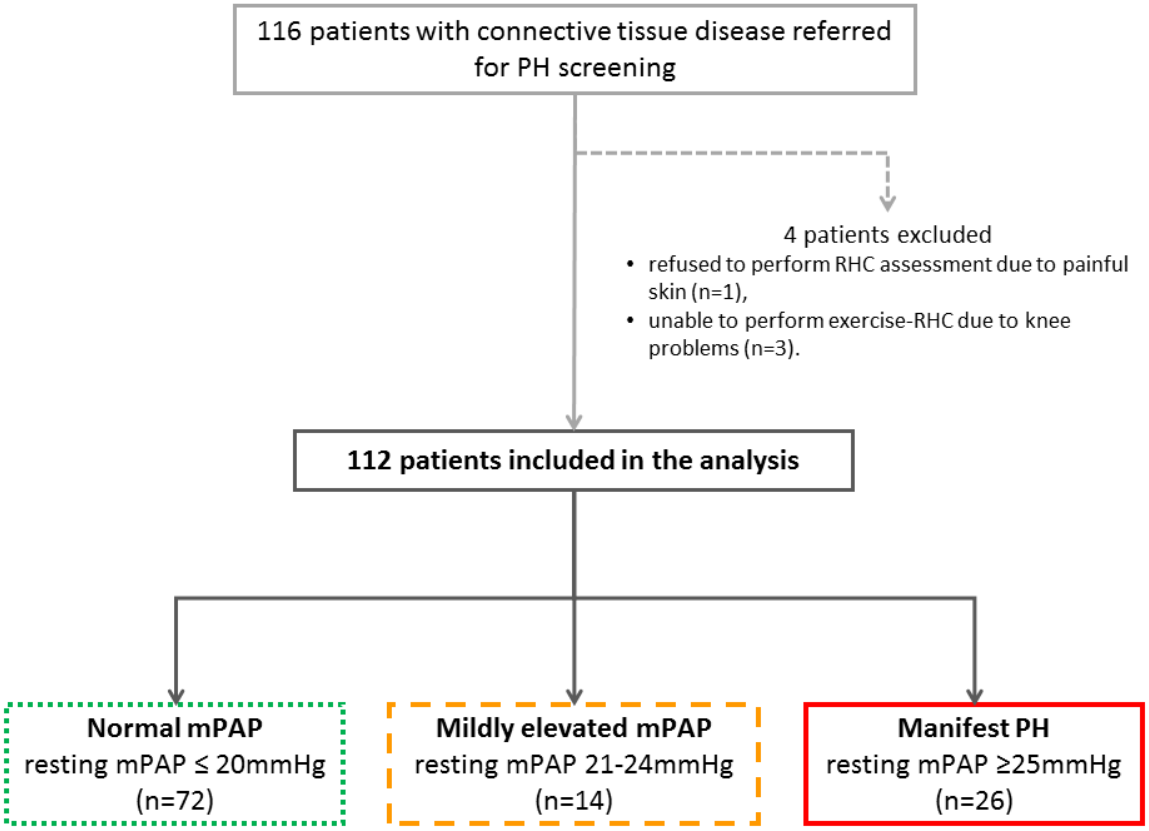


Figure 2: Pearson's correlation analysis of PAC vs. 6MWD

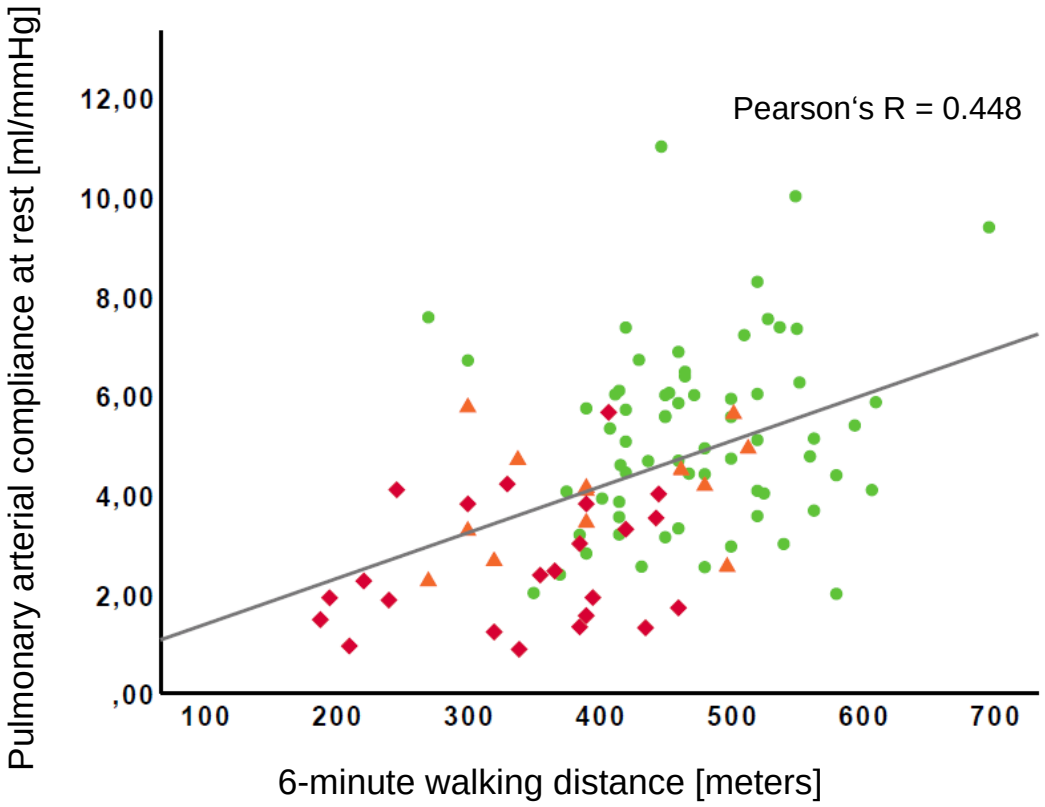
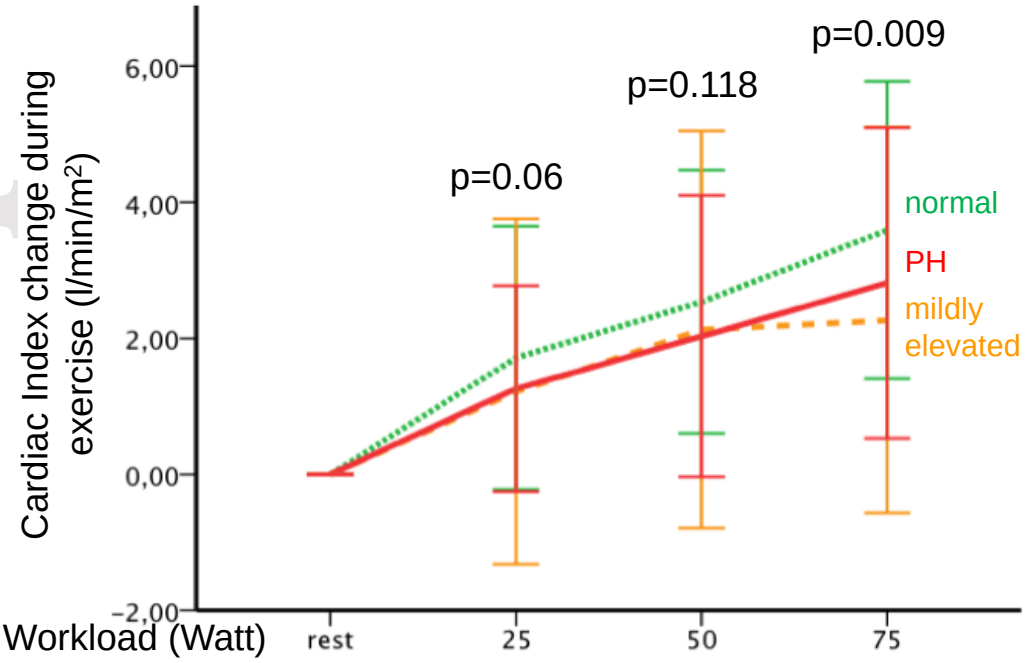
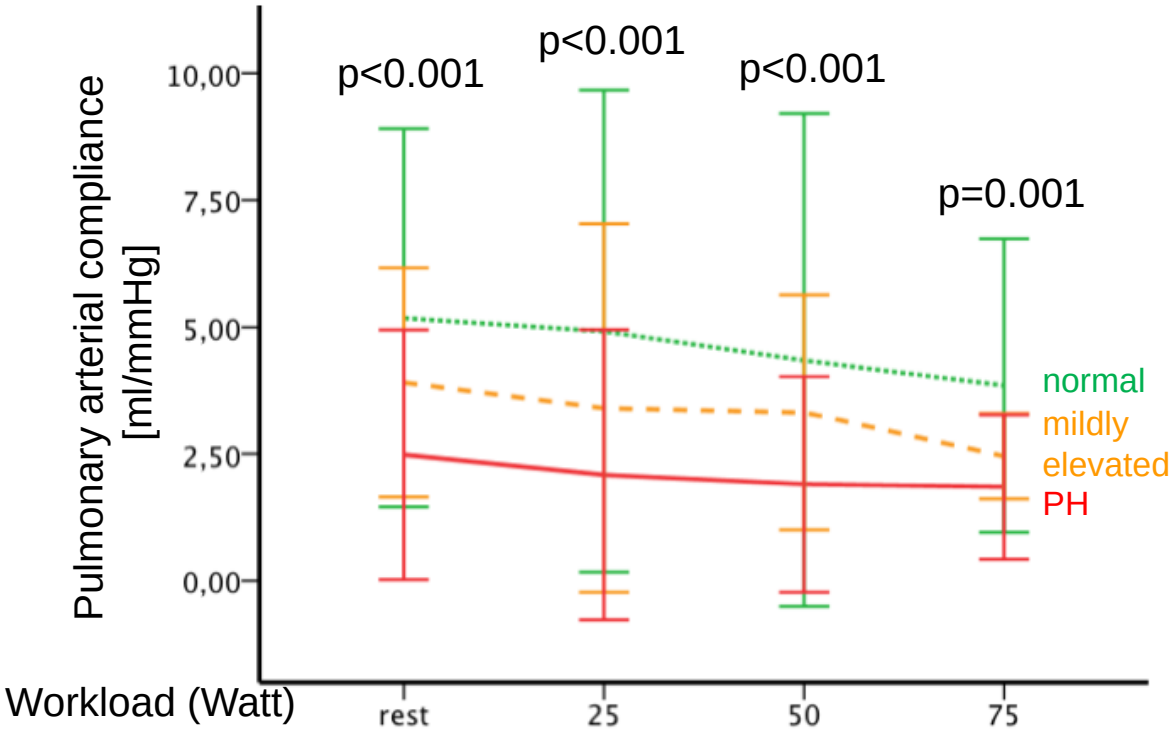


Figure 3: Cardiac Index increase over workload levels



N	rest	25	50	75
Normal	72	69	71	49
Mildly elevated	14	14	11	7
PH	26	24	19	7

Figure 4: PAC over workload levels



N	rest	25	50	75
Normal	69	66	70	48
Mildly elevated	14	13	10	6
PH	26	22	19	6

References

1. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2009;179:151-7.
2. Coghlan JG. Stress echocardiography and Cochin Risk Prediction Score for the prediction of pulmonary arterial hypertension in scleroderma: not yet ready for prime time. Arthritis Rheum 2013;65:2236-9.
3. Ngian GS, Stevens W, Prior D, Gabbay E, Roddy J, Tran A, et al. Predictors of mortality in connective tissue disease-associated pulmonary arterial hypertension: a cohort study. Arthritis Res Ther 2012;14:R213.
4. Lefevre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum 2013;65:2412-23.
5. Steen V, Chou M, Shanmugam V, Mathias M, Kuru T, Morrissey R. Exercise-induced pulmonary arterial hypertension in patients with systemic sclerosis. Chest 2008;134:146-51.
6. Kovacs G, Avian A, Tscherner M, Foris V, Bachmaier G, Olschewski A, et al. Characterization of patients with borderline pulmonary arterial pressure. Chest 2014;146:1486-93.
7. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62:D42-50.
8. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903-75.
9. Visovatti SH, Distler O, Coghlan JG, Denton CP, Grunig E, Bonderman D, et al. Borderline pulmonary arterial pressure in systemic sclerosis patients: a post-hoc analysis of the DETECT study. Arthritis Res Ther 2014;16:493.
10. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. Eur Respir J 2009;34:888-94.
11. Valerio CJ, Schreiber BE, Handler CE, Denton CP, Coghlan JG. Borderline mean pulmonary artery pressure in patients with systemic sclerosis: transpulmonary gradient predicts risk of developing pulmonary hypertension. Arthritis Rheum 2013;65:1074-84.
12. Hoeper MM. Definition, classification, and epidemiology of pulmonary arterial hypertension. Semin Respir Crit Care Med 2009;30:369-75.
13. Lewis GD, Bossone E, Naeije R, Grunig E, Saggar R, Lancellotti P, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. Circulation 2013;128:1470-9.
14. Grunig E, Tiede H, Enyimayew EO, Ehlken N, Seyfarth HJ, Bossone E, et al. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. Circulation 2013;128:2005-15.
15. Blumberg FC, Arzt M, Lange T, Schroll S, Pfeifer M, Wensel R. Impact of right ventricular reserve on exercise capacity and survival in patients with pulmonary hypertension. Eur J Heart Fail 2013;15:771-5.
16. Chaouat A, Sitbon O, Mercy M, Poncot-Mongars R, Provencher S, Guillaumot A, et al. Prognostic value of exercise pulmonary haemodynamics in pulmonary arterial hypertension. Eur Respir J 2014;44:704-13.
17. Thenappan T, Prins KW, Pritzker MR, Scandurra J, Volmers K, Weir EK. The Critical Role of Pulmonary Arterial Compliance in Pulmonary Hypertension. Ann Am Thorac Soc 2016;13:276-84.
18. Jain P, Rao S, Macdonald P, Kotlyar E, Jabbour A, Hayward C, et al. Diagnostic Performance of Pulmonary Capacitance at Rest and During Exercise in Idiopathic Pulmonary Arterial Hypertension. Heart Lung Circ 2017.

19. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.
20. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
21. Kovacs G, Avian A, Pienn M, Naeije R, Olschewski H. Reading pulmonary vascular pressure tracings. How to handle the problems of zero leveling and respiratory swings. Am J Respir Crit Care Med 2014;190:252-7.
22. Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, et al. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. Eur Respir J 2017;50.
23. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657-62.
24. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788-94.
25. Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340-9.
26. Brimioulle S, Wauthy P, Ewalenko P, Rondelet B, Vermeulen F, Kerbaul F, et al. Single-beat estimation of right ventricular end-systolic pressure-volume relationship. Am J Physiol Heart Circ Physiol 2003;284:H1625-30.
27. Spruijt OA, Bogaard HJ, Heijmans MW, Lely RJ, van de Veerdonk MC, de Man FS, et al. Predicting pulmonary hypertension with standard computed tomography pulmonary angiography. Int J Cardiovasc Imaging 2015;31:871-9.
28. Hsu S, Houston BA, Tampakakis E, Bacher AC, Rhodes PS, Mathai SC, et al. Right Ventricular Functional Reserve in Pulmonary Arterial Hypertension. Circulation 2016;133:2413-22.
29. Chia EM, Lau EM, Xuan W, Celermajer DS, Thomas L. Exercise testing can unmask right ventricular dysfunction in systemic sclerosis patients with normal resting pulmonary artery pressure. Int J Cardiol 2016;204:179-86.
30. Latus H, Gummel K, Diederichs T, Bauer A, Rupp S, Kerst G, et al. Aortopulmonary collateral flow is related to pulmonary artery size and affects ventricular dimensions in patients after the fontan procedure. PLoS One 2013;8:e81684.
31. Wink J, de Wilde RB, Wouters PF, van Dorp EL, Veering BT, Versteegh MI, et al. Thoracic Epidural Anesthesia Reduces Right Ventricular Systolic Function With Maintained Ventricular-Pulmonary Coupling. Circulation 2016;134:1163-75.
32. Sanz J, Kariisa M, Dellegrottaglie S, Prat-Gonzalez S, Garcia MJ, Fuster V, et al. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. JACC Cardiovasc Imaging 2009;2:286-95.
33. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, et al. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol 2013;62:D22-33.
34. Rich S. Right ventricular adaptation and maladaptation in chronic pulmonary arterial hypertension. Cardiol Clin 2012;30:257-69.
35. Sutendra G, Michelakis ED. The metabolic basis of pulmonary arterial hypertension. Cell Metab 2014;19:558-73.
36. Chemla D, Lau EM, Papelier Y, Attal P, Herve P. Pulmonary vascular resistance and compliance relationship in pulmonary hypertension. Eur Respir J 2015;46:1178-89.
37. Mahapatra S, Nishimura RA, Oh JK, McGoon MD. The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. J Am Soc Echocardiogr 2006;19:1045-50.
38. Medrek SK, Kloefkorn C, Nguyen DTM, Graviss EA, Frost AE, Safdar Z. Longitudinal change in pulmonary arterial capacitance as an indicator of prognosis and response to therapy and in pulmonary arterial hypertension. Pulm Circ 2017;7:399-408.

39. Ghio S, D'Alto M, Badagliacca R, Vitulo P, Argiento P, Mule M, et al. Prognostic relevance of pulmonary arterial compliance after therapy initiation or escalation in patients with pulmonary arterial hypertension. Int J Cardiol 2017;230:53-8.
40. Kovacs G, Maier R, Aberer E, Brodmann M, Graninger W, Kqiku X, et al. Pulmonary arterial hypertension therapy may be safe and effective in patients with systemic sclerosis and borderline pulmonary artery pressure. Arthritis Rheum 2012;64:1257-62.
41. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Respir J 2015; 46(6): 1855-6.

42. Hsu S, Kokkonen-Simon KM, Kirk JA, Kolb TM, Damico RL, Mathai SC, et al. Right Ventricular Myofilament Functional Differences in Humans With Systemic Sclerosis-Associated Versus Idiopathic Pulmonary Arterial Hypertension.Circulation 2018;137(22):2360-2370.

43. Tedford RJ, Mudd JO, Girgis RE, Mathai SC, Zaiman AL, Housten-Harris T, et al. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. Circ Heart Fail 2013:6(5):953-63.

44. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, et al. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J. 2015; 46:728-37.

45. Lau EM, Godinas L, Sitbon O, Montani D, Savale L, Jaïs X, et al. Resting pulmonary artery pressure of 21-24 mmHg predicts abnormal exercise haemodynamics. Eur Respir J. 2016; 47:1436-44

46. Heresi GA, Minai OA, Tonelli AR, Hammel JP, Farha S, Parambil JG, Dweik RA. Clinical characterization and survival of patients with borderline elevation in pulmonary artery pressure. Pulm Circ 2016; 3: 916-925.

47. Oliveira RKF, Faria-Urbina M, Maron BA, Santos M, Waxman AB, Systrom DM. Functional impact of exercise pulmonary hypertension in patients with borderline resting pulmonary arterial pressure. Pulm Circ. 2017; 7:654-665.