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Pulmonary vascular disease and pulmonary exercise hemodynamics in patients with Sjögren's syndrome – a cross-sectional study

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Sjögren's syndrome is an autoimmune disease affecting exocrine glands leading to a sicca-syndrome (1). When occurring with other autoimmune diseases it is termed secondary Sjögren's syndrome. Systemic manifestations such as pulmonary vascular disease (PVD) including pulmonary arterial hypertension (PAH) are associated with poor outcome (2). Data regarding the frequency of PAH are mainly limited to Asian registry-collectives (3–5).

Of note, due to increasing evidence for the prognostic relevance of mildly elevated mean pulmonary arterial pressure (mPAP) within the range of 21–24 mmHg, the definition of pulmonary hypertension (PH) was recently revised (6,7). Furthermore, as pulmonary hemodynamics during exercise are associated with clinical outcome (8,9), the term exercise PH (EPH) was recently reintroduced (7). So far, no data exists regarding the prevalence of EPH and mild PH in Sjögren's syndrome. Hence, this study aimed to assess the frequency of PVD based on most recent guidelines, using a screening algorithm with resting- and exercise echocardiography and right heart catheterization (RHC).

Consecutive patients with diagnosed Sjögren's syndrome from rheumatological and ophthalmological outpatient clinics were invited (10). Exclusion criteria included uncontrolled systemic arterial hypertension, recent pulmonary embolism or myocardial infarction, LV ejection fraction (LVEF) <50%, diastolic dysfunction ≥grade 2, significant valvular heart disease or pregnancy/breast-feeding. The study was approved by the Ethics Committee of the Medical University of Graz (26-446 ex 13/14) and registered at clinical trials.gov (NCT02752269). Patients underwent assessment for symptoms, pulmonary function testing, resting- and exercise-echocardiography combined with cardiopulmonary-exercise-testing (CPET) using a cycle ergometer with stepwise increase of workload (25-Watt-increase every 2 minutes). Exercise echocardiography was performed in semi supine left-tilted position. At each step, systolic PAP (sPAP) and velocity-time-integral derived cardiac output (CO) were assessed. SPAP was estimated by using the simplified Bernoulli equation and by adding an estimate of right atrial pressure as previously described (11). Estimated mPAP was calculated from sPAP as 0.61*x*sPAP+2 (12). In patients with resting sPAP≥38 mmHg (estimated invasive mPAP≥25 mmHg), RHC was recommended due to suspected more severe PH and potential indication for treatment. Further, in subjects with suspected mild PH (mPAP: 21-24 mmHg) or EPH, resting and exercise RHC was suggested in case of relevant exercise limitation or exercise dyspnoea (for decision tree please and hemodynamic criteria please see Figure 1A). At RHC, CO was assessed using thermodilution. The mPAP/CO-slope was calculated by (peak–resting mPAP)/(peak–resting CO). According to the recent recommendations, PH was defined as RHC-derived mPAP>20 mmHg. Pre-capillary PH was defined as mPAP>20 mmHg, PAWP≤15 mmHg and PVR>2 WU (13). PAH was defined as pre-capillary PH and exclusion of other PH groups and EPH was defined as mPAP/CO-slope>3 mmHg/L/min (13). Data are expressed as means ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Categorical data are presented as absolute and relative frequencies. For in-between group comparisons, T-Tests and U-Tests were used. Categorical variables were analyzed using Fisher's exact test or Chi2-test. A p-value <0.05 was considered significant. Statistical analysis was performed using IBM SPSS Statistics (Release 20.0.0. 2011. Chicago (IL), USA: SPSS Inc., an IBM Company).

Two patients were excluded after screening due to newly diagnosed severe exercise induced systemic hypertension (n=1) and moderate to severe mitral insufficiency (n=1). Characteristics of the remaining 81 patients are shown in Table 1. Forty-four (54%) patients had primary and 37 (46%) secondary Sjögren's syndrome. In 4 (5%) cases, sPAP could not be assessed at rest due to missing tricuspid regurgitation signal. In 13 (16%) patients exercise echocardiographic mPAP/CO slope could not be calculated due to inadequate mPAP or CO estimates. No relevant differences were detected between patients with primary- and secondary Sjögren's

syndrome (Supplement Table 1). Pulmonary function testing revealed well-preserved lung function (Table 1).

In the overall collective, 20 (25%) patients had an echocardiographic estimated mPAP/CO-slope>3mmHg/L/min and additional seven patients had abnormal peak exercise sPAP and TPR. In total, 27 patients were classified as possible EPH. N=4/27 patients with suspected EPH additionally showed an echocardiographic resting sPAP≥38mmHg (suspected severe PH) and 7 had a resting sPAP of 31-38 mmHg (suspected mild PH). These 11 patients were not grouped in the “suspected EPH group” but in the group “suspected severe PH” and “suspected mild PH”, respectively. The remaining 16 patients were grouped in the “suspected EPH group”. There was no difference in the frequency of “suspected EPH” in patients with secondary vs. primary Sjögren’s syndrome. Patients with abnormal echocardiographic hemodynamics were significantly older (65±10 years vs. 55±10 years, p<0.001), had a higher NT-proBNP (145 (71–343) pg/ml vs. 74 (44–110) pg/ml, p=0.002) and significantly lower TAPSE/sPAP-ratio (0.8±0.2 mm/mmHg vs. 1.0±0.2 mm/mmHg, p<0.001) (Supplement Table 2). When comparing patients without echocardiographic signs of PVD with those 29 subjects who were at risk for PVD we found no significant differences in the EULAR Sjögren's syndrome disease activity index (ESSDAI) (Supplement Table 2).

Final screening results are presented in Figure 1 B. Overall, out of 10 patients undergoing RHC, PAH was finally confirmed in two patients (2%) and EPH was confirmed in eight (10%) patients. Six patients showed an increase of PAWP > 21 mmHg during stress testing, indicating possible latent left heart disease. Pulmonary hemodynamics of all patients undergoing RHC are provided in Supplement Table 3. Out of the two patients with PAH, one had primary and the other had secondary Sjögren’s syndrome.

PAH is complicating several autoimmune disorders, including Sjögren’s syndrome and is associated with increased mortality (2,7). According to recent registry data, the prevalence of PAH in adults is 12–268 in 1.000.000 and approximately 15-30% have PAH due to CTD (14,15). According to the French PAH registry the prevalence of CTD among PAH patients was 15% with systemic sclerosis and systemic lupus erythematosus as leading causes (14). In an echocardiography study 5/47 (11%) patients with primary Sjögren’s syndrome had PH (5). However, in this study, only five patients had a sPAP>35 mmHg and no RHC was performed to confirm PAH. Prevalence of PAH in Sjögren’s has been more frequently reported in Asian patient collectives, representing 16% of all PAH cases in connective tissue disease (16). According to a recent retrospective PH register study from Japan out of 142 patients diagnosed with PAH, only one patient was initially diagnosed with PAH associated with primary Sjögren’s syndrome (3). In our study out of four patients with non-invasive SPAP≥38 mmHg,

RHC confirmed PAH in only two patients and PAH was only mild, not meeting the indication for targeted PAH therapy.

Besides pulmonary resting hemodynamics we also focused on pathological pulmonary exercise hemodynamics as there is increasing evidence for the clinical relevance of EPH (8) and no data have been available so far on pulmonary exercise hemodynamics in Sjögren's syndrome. Assessment of pulmonary exercise hemodynamics may also be possible non-invasively by using exercise echocardiography. Although this may be limited by inadequate estimations of PAP and CO at peak exercise, recent studies supported the prognostic value of the method (17). Accordingly, recent guidelines recommended to consider exercise echocardiography or CPET in symptomatic patients with SSc to aid decisions to perform RHC (7).

To best of our knowledge this was the first study to systematically implement exercise-echocardiography in the screening for PVD in Sjögren's syndrome. The underlying mechanisms of EPH were heterogenous in our collective with pre- and post-capillary phenotypes (18). Patients with EPH suspected by echocardiography were significantly older and had higher resting E/e' suggesting subclinical diastolic dysfunction as an additional contributing factor for pathological exercise hemodynamics. This was also indicated by steeper increase of PAWP during exercise RHC. Left

Previous publications showed significantly worse prognosis of patients with systemic sclerosis when complicated by secondary Sjögren's syndrome (19). To which extent this is caused by a higher prevalence of PVD is unknown. Accordingly, we decided not only to include patients with primary- but also with secondary Sjögren's syndrome. Interestingly we found a balanced prevalence of PH between primary- secondary Sjögren's syndrome.

Based on our observations, assessment of PVD may be useful in symptomatic patients with Sjögren's Syndrome. So far, no data exist regarding the optimal management of patients diagnosed with EPH or mild PH. However, such patients may be at risk to progress to more severe PAH (20). In addition, even a mild elevation of PAP is associated with poor outcome in patients at risk for PH (6). Current guidelines recommend close follow-up of these patients (7,13). There is no evidence for the safety and efficacy of PAH drugs in patients with exercise PH or mild PH (mPAP < 25mmHg) from randomized controls trials.

Our study is limited by its single center character. Due to limited therapeutic consequences and ethical reasons, RHC could not be performed in all patients with suspected EPH. Accordingly, RHC was only offered in case of relevant symptoms. Still, to the best of our knowledge, this is the first prospective cross-sectional study, systematically screening a large number of patients with Sjögren's syndrome for the presence of PVD including mild PH and

EPH. The prevalence of PAH in patients with primary- and secondary Sjögren's syndrome in patients of European ancestry was low. Suspected EPH was relatively frequent, warranting follow-up studies concerning the development of severe PVD or relevant left heart disease in this patient collective.

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References

1. Fox RI. Sjögren's syndrome. Lancet Lond Engl. 2005 Jul 23;366(9482):321–31.

2. Liu Z, Yang X, Tian Z, Qian J, Wang Q, Zhao J, et al. The prognosis of pulmonary arterial hypertension associated with primary Sjögren's syndrome: a cohort study. Lupus. 2018 Jun;27(7):1072–80.

3. Sato T, Hatano M, Iwasaki Y, Maki H, Saito A, Minatsuki S, et al. Prevalence of primary Sjögren's syndrome in patients undergoing evaluation for pulmonary arterial hypertension. PloS One. 2018;13(5):e0197297.

4. Zhao Y, Li Y, Wang L, Li XF, Huang CB, Wang GC, et al. Primary Sjögren syndrome in Han Chinese: clinical and immunological characteristics of 483 patients. Medicine (Baltimore). 2015 Apr;94(16):e667.

5. Kobak S, Kalkan S, Kirilmaz B, Orman M, Ercan E. Pulmonary Arterial Hypertension in Patients with Primary Sjögren's Syndrome. Autoimmune Dis. 2014;2014:710401.

6. Douschan P, Kovacs G, Avian A, Foris V, Gruber F, Olschewski A, et al. Mild Elevation of Pulmonary Arterial Pressure as a Predictor of Mortality. Am J Respir Crit Care Med. 2017 Nov 3;

7. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2022 Aug 25;2200879.

8. Douschan P, Avian A, Foris V, Sassmann T, Bachmaier G, Rosenstock P, et al. Prognostic Value of Exercise- as Compared to Resting Pulmonary Hemodynamics in Patients with Normal or Mildly Elevated Pulmonary Arterial Pressure. Am J Respir Crit Care Med. 2022 Aug 4;

9. Kovacs G, Humbert M, Avian A, Lewis GD, Ulrich S, Vonk Noordegraaf A, et al. Prognostic relevance of exercise pulmonary hypertension: results of the multicentre PEX-NET Clinical Research Collaboration. Eur Respir J. 2024 Dec;64(6):2400698.

10. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol Hoboken NJ. 2017 Jan;69(1):35–45.

11. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography. J Am Soc Echocardiogr. 2010 Jul;23(7):685–713.

12. Chemla D, Castelain V, Humbert M, Hébert JL, Simonneau G, Lecarpentier Y, et al. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. Chest. 2004 Oct;126(4):1313–7.

13. Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 2024 Aug 29;2401324.

14. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med. 2006 May 1;173(9):1023–30.

15. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. Eur Respir J. 2007 Dec;30(6):1103–10.

16. Hao YJ, Jiang X, Zhou W, Wang Y, Gao L, Wang Y, et al. Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. Eur Respir J. 2014 Oct;44(4):963–72.

17. Gargani L, Pugliese NR, De Biase N, Mazzola M, Agoston G, Arcopinto M, et al. Exercise Stress Echocardiography of the Right Ventricle and Pulmonary Circulation. J Am Coll Cardiol. 2023 Nov 21;82(21):1973–85.

18. Reddy YNV, Obokata M, Wiley B, Koepp KE, Jorgenson CC, Egbe A, et al. The haemodynamic basis of lung congestion during exercise in heart failure with preserved ejection fraction. Eur Heart J. 2019 Dec 1;40(45):3721–30.

19. Scherlinger M, Lutz J, Galli G, Richez C, Gottenberg JE, Sibilia J, et al. Systemic sclerosis overlap and non-overlap syndromes share clinical characteristics but differ in prognosis and treatments. Semin Arthritis Rheum. 2021 Feb;51(1):36–42.

20. Assad TR, Maron BA, Robbins IM, Xu M, Huang S, Harrell FE, et al. Prognostic Effect and Longitudinal Hemodynamic Assessment of Borderline Pulmonary Hypertension. JAMA Cardiol. 2017 Oct 25;

Figures:

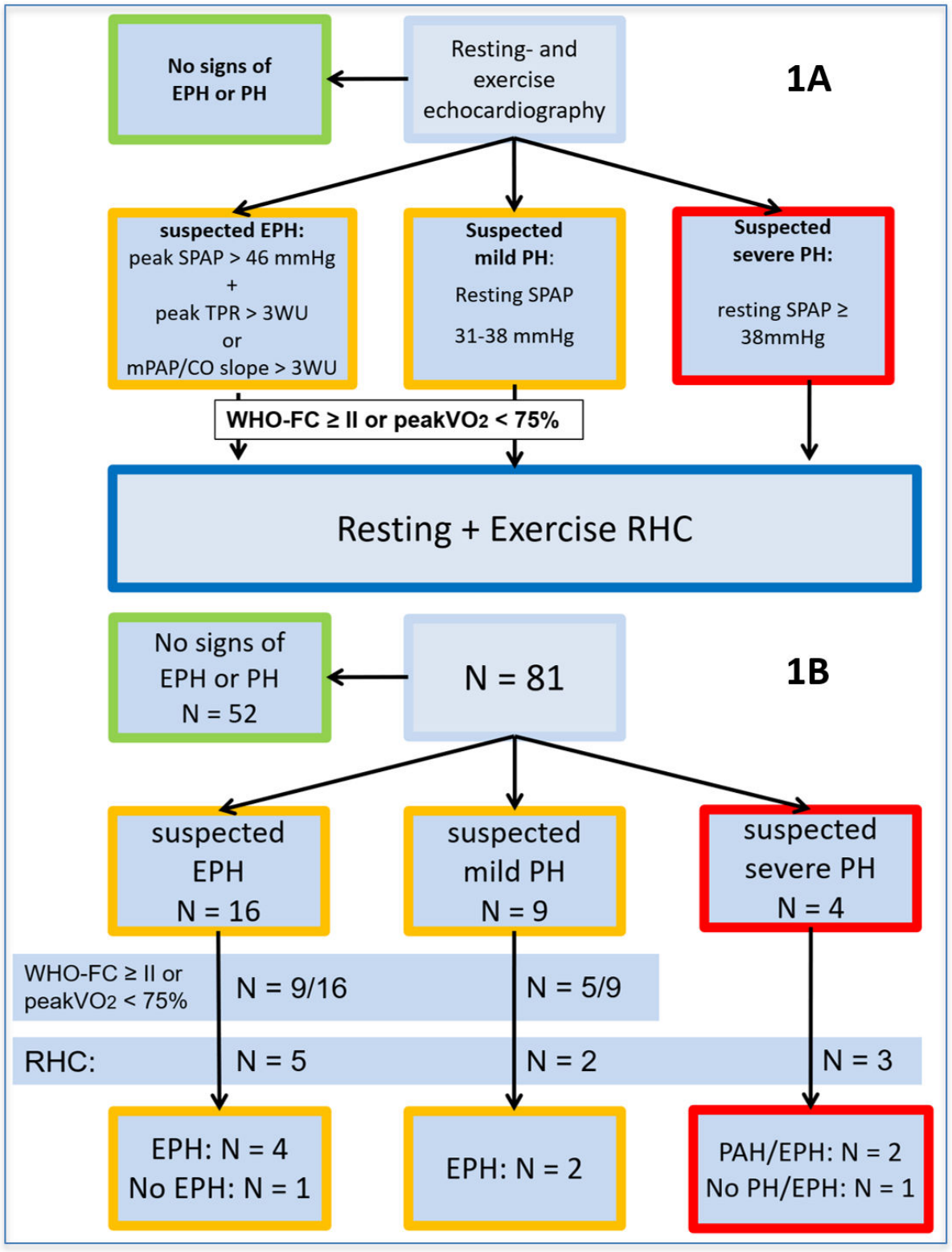

Figure 1: A: Screening algorithm for pulmonary vascular disease; Abbreviations: PVD: pulmonary vascular disease, PH: pulmonary hypertension, EPH: exercise pulmonary hypertension, mPAP: mean pulmonary arterial pressure; CO: cardiac output; sPAP: systolic pulmonary arterial pressure, WHO-FC: World Health Organization functional class, peakVO_2: peak oxygen uptake, RHC: right heart catheterization; B: Screening Results; Explanation: The light blue box represents the overall cohort. In 13 (16%) patients echocardiographic mPAP/CO slope could not be

calculated due to a lack of adequate mPAP or CO estimates from exercise echocardiography, in these patients echocardiographic sPAP > 46 mmHg (corresponding to a mPAP > 30 mmHg) and TPR > 3WU was used to rise suspicion for EPH. Green box: no signs of EPH or mild PH according to our screening algorithm; of note, 2/29 patients did not undergo exercise testing. Yellow box left: echocardiographic mPAP/CO slope > 3mmHg/l/min or echocardiographic sPAP > 46mmHg and echocardiographic TPR > 3WU at peak exercise. Yellow box middle: echocardiographic resting sPAP 31-38 mmHg. Red box: echocardiographic resting sPAP ≥ 38 mmHg. Abbreviations: PH: pulmonary hypertension, PAH: pulmonary arterial hypertension, EPH: exercise pulmonary hypertension, PVD: pulmonary vascular disease; mPAP: mean pulmonary arterial pressure; sPAP: systolic pulmonary arterial pressure; RHC: right heart catheterization; WHO-FC: World Health Organization functional class, N= number; peakVO2: peak oxygen uptake, TPR= total pulmonary resistance;

Table 1: Patient charateristics

Variable:		Mean ± SD / Median (IQR) No. (%)
Age (yr.)		58 (51 - 67)
BMI		24 (22 - 27)
Sex	Female	77 (91%)
	Male	4 (9%)
Primary Sjögren:		44 (54%)
Secondary Sjögren:		37 (46%)
	SSc	13 (16%)
	SLE	9 (12%)
	RA	5 (6%)
	MCTD	5 (6%)
	Others	5 (6%)
WHO-FC	I	50 (62%)
	II	30 (37%)
	III	1 (1%)
	IV	-
NT-proBNP (pg/ml)		79 (60 - 145)
FEV_1 (%predicted)		106 (96 - 117)
TLC (%predicted)		107 ± 16
DLCOcSB (%predicted)		90 ± 17
DLCOcVA (%predicted)		88 (79 - 100)
PaO_2 (mmHg)		85 ± 9
$PaCO_2$ (mmHg)		35 ± 3
$AaDO_2$ (mmHg)		20 ± 10
Echocardiography		
sPAP (mmHg)		25 (23 - 29)
TAPSE (mm)		23 ± 4
TAPSE/sPAP ratio		0.9 (0.8-1.0)
CO (L/min)		4.74 ± 0.96
E/e'		7.5 (6.1 – 9.4)
Exercise Echocardiography		
$sPAP_{peak}$ (mmHg)		44 ± 12
CO_{peak} (L/min)		9.5 ± 2.3
TPR_{peak} (WU)		2.9 (2.4 - 3.4)
$TAPSE/sPAP_{peak}$ ratio		0.7 (0.5-0.8)
mPAP/CO slope (mmHg/L/min)		2.3 (1.5 - 3.1)
Peak VO_2 (%predicted)		78 ± 24
min EqO_2 ()		22.9 (21.3 – 25.1)
min $EqCO_2$ ()		28.6 ± 3.6
6MWD (m)		459 ±61

Normally distributed variables are expressed as mean ± SD, non-normally distributed variables are expressed as median and IQR; Abbreviations: SSc: systemic sclerosis, SLE: systemic lupus erythematodes, RA: rheumatoid arthritis, MCTD: mixed CTD, WHO-FC: World Health Organization functional class, NT-proBNP: N terminal pro

brain natriuretic peptide, FEV_1: forced expiratory volume at 1 second, TLC: total pulmonar capacity, DLCOcSB: single breath diffusion capacity for carbon monoxide, DLCOcVA: DLCO corrected for alveolar volume, PaO_2: arterial oxygen partial pressure, $PaCO_2$: arterial carbon dioxide partial pressure, $AaDO_2$: arterial-alveolar oxygen partial pressure difference, E/E': early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity; SPAP: systolic pulmonary arterial pressure, TPR: total pulmonary resistance; TAPSE: tricuspid annular plane systolic excursion, mPAP: mean pulmonary arterial pressure; CO: cardiac output, $peakVO_2$: peak oxygen uptake, EqO_2: ventilatory equivalent for O2, $EqCO_2$: ventilatory equivalent for CO_2, 6MWD: 6.minute walking distance.

Supplement

Supplement Table 1: Differences between primary- and secondary Sjögren's syndrome.

Variable:	Primary Sjögren (N=44)	Secondary Sjögren (N=37)	p-value
Age	57 ± 10	59 ± 11	p=0.325
BMI	23 (22 - 26)	24 (22 - 28)	p=0.22
ESSDAI Score	0.5 (0-3.75)	0 (0-2)	p=0.131
NT-proBNP (pg/ml)	75 (52 - 144)	86 (63 - 182)	p=0.525
FEV1 (%predicted)	107 (101 - 118)	104 (86 - 110)	p=0.042
TLC (%predicted)	110 ± 15	103 ± 17	p=0.027
DLCOcSB (%predicted)	95 ± 16	83 ± 16	p=0.002
DLCOcVA (%predicted)	87 (80 - 98)	89 (78 - 95)	p=0.446
sPAP (mmHg)	23 (22 - 28)	25 (23 - 29)	p=0.067
TAPSE (mm)	23 (22 - 28)	23 (21 - 25)	p=0.628
CO (L/min)	4.7 ± 0.9	4.8 ± 1.0	p=0.667
E/e'	7.2 (6.0 – 8.7)	7.9 (6.2 – 9.6)	p=0.303
sPAPpeak (mmHg)	43 ± 12	46 ± 12	p=0.389
COpeak (mmHg)	9.7 ± 2.3	9.3 ± 2.4	p=0.426
TPRpeak (WU)	2.8 (2.3 - 3.3)	3.1 (2.4 - 3.6)	p=0.143
mPAP/CO-slope (mmHg/L/min)	2.1 (1.2 - 2.9)	2.6 (1.7 - 3.6)	p=0.103
suspected EPH n (%)	8 (18%)	8 (21%)	p=0.59
Signs of PVD n (%)	14 (32%)	15 (41%)	p=0.488
Peak VO_2 (%predicted)	84 (65 -102)	71 (55 - 85)	p=0.084
min EqO_2	22.8 (21.1 – 24.6)	23.1 (21.5 – 26.3)	p=0.308
min $EqCO_2$	27.7 (26.2 – 29.0)	29.4 (27.3 – 31.4)	p=0.04
6MWD (m)	471 ± 71	432 ± 73	p=0.021

Normally distributed variables are expressed as mean ± SD, non-normally distributed variables are expressed as median and IQR; Abbreviations: ESSDAI: EULAR Sjögren's syndrome disease activity index; NT-proBNP: N terminal pro brain natriuretic peptide, FEV1: forced expiratory volume at 1 second, TLC: total lung capacity, DLCOcSB: single breath diffusion capacity for carbon monoxide, DLCOcVA: DLCO corrected for alveolar volume, SPAP: systolic pulmonary arterial pressure, TAPSE: tricuspid annular plane systolic excursion, CO: cardiac output, Screening Results; PH: pulmonary hypertension, EPH: exercise pulmonary hypertension, peakVO_2: peak oxygen uptake, EqO_2: ventilatory equivalent for O_2, $EqCO_2$: ventilatory equivalent for CO_2, 6MWD: 6 minute walking distance;

Supllement Table 2: Patients with normal vs. abnormal resting- and exercise hemodynamics by echocardiography

Variable	No signs of PVD (N=52)	Signs of PVD (N=29)	p-value
Age	54 ± 9	64 ± 10	p<0.001
BMI	23.9 (21.9-27.9)	23.8 (21.8-25.2)	p=0.171
NT-proBNP (pg/ml)	73 (39-107)	144 (69-342)	p<0.001
ESSDAI score N=79	0 (0-2)	0 (0-5)	p=0.151
CENP antibodies N=71, N (%)	8/45 (18%)	6/26 (23%)	p=0.589
Anti-Ro/SSA antibodies N=72, N (%)	37/46 (80%)	15/26 (58%)	p=0.039
Rheumatoid factor N=55, N (%)	18/36 (50%)	8/19 (42%)	p=0.577
Immunoglobulin G N=47	14.2 (12.0-16.6)	13.3 (10.3-19.5)	p=0.599
Complement factor C3 N=62	1.05 (0.93-1.19)	1.04 (0.89-1.17)	p=1.000
Complement factor C4 N=62	0.17 (0.13-0.22)	0.17 (0.14-0.24)	p=1.000
FVC (%predicted)	114 ± 20	108 ± 15	p=0.171
FEV_1 (%predicted)	106 ± 18	99 ± 18	p=0.076
FEV_1/FVC (%predicted)	79 ± 5	75 ± 9	p=0.025
TLC (%predicted)	109 ± 16	103 ± 16	p=0.086
DLCOcSB (%predicted)	89 ± 17	90 ± 18	p=0.813
DLCOcVA (%predicted)	88 ± 15	93 ± 13	p=0.117
Resting Echocardiography			
sPAP at rest (mmHg)	23 (21-25)	29 (25-34)	p<0.001
TAPSE at rest (mm)	23 (21-26)	24 (22-26)	p=0.424
TAPSE/sPAP ratio at rest	0.99 (0.88-1.11)	0.82 (0.69-0.92)	p<0.001
CO at rest (L/min)	4.7 (4.2-5.4)	4.6 (3.8-5.5)	p=0.431
E/e' at rest	6.9 (5.9-8.5)	8.4 (7.4-10.8)	p<0.001
Exercise Echocardiography			
$sPAP_{peak}$	38 (33-43)	55 (50-58)	p<0.001
$TAPSE_{peak}$	29 (27-31)	29 (25-31)	p=0.252
$TAPSE/sPAP_{ratio\ peak}$	0.78 (0.67-0.96)	0.50 (0.44-0.64)	p<0.001
CO_{peak}	10.6 (9.0-12.3)	8.9 (7.9-10.4)	p=0.001
TPR_{peak} (WU)	2.4 (2.3-2.9)	3.9 (3.4-5.1)	p<0.001
mPAP/CO-slope	1.7 (1.2-2.2)	3.3 (2.7-4.8)	p<0.001
Exercise Testing			
Peak exercise level (Watt)	100 (75-125)	75 (75-100)	p=0.002
Peak VO_2 (%predicted)	85 (69-104)	90 (75-107)	p=0.455
min EqO_2	22.8 (21.3-24.7)	23.2 (20.4-26-3)	p=0.396
min $EqCO_2$	28.2 (26.2-29.9)	29 (27-31)	p=0.144
6MWD (m)	467 (433-502)	456 (367-489)	p=0.139

Differences between patients without signs of pulmonary vascular disease (PVD: suspected more severe PH, mild PH or EPH) and with signs of PVD, respectively, according to our screening algorithm. Normally distributed variables are expressed as mean ± SD, non-normally distributed variables are expressed as median and Interquartile Range (IQR, 25-75); Abbreviations: BMI: body mass index; NT-proBNP: N terminal pro brain natriuretic peptide, ESSDAI: EULAR Sjögren's syndrome disease activity index; Anti-Ro/SSA: Sjögren's-Syndrome-related Antigen A autoantibodies; FEV_1: forced expiratory volume at 1 second, TLC: total lung capacity, DLCOcSB: single breath diffusion capacity for carbon monoxide, DLCOcVA: DLCO corrected for alveolar volume, E/E': early diastolic transmitral flow velocity to early diastolic mitral annular tissue velocity; mPAP: mean pulmonary arterial pressure; sPAP: systolic pulmonary arterial pressure, TPR: total pulmonary resistance, TAPSE: tricuspid annular plane systolic excursion, CO: cardiac output, Screening Results; peak VO_2: peak oxygen uptake, EqO_2: ventilatory equivalent for O_2, $EqCO_2$: ventilatory equivalent for CO_2, 6MWD: 6.minute walking distance;

Supplement Table 3: Pulmonary resting- and exercise hemodynamics assessed by RHC.

RHC at rest					RHC at peak exercise						
mPAP (mmHg)	PAWP (mmHg)	RAP (mmHg)	PVR (WU)	CO (l/min)	Max. work load (Watt)	mPAPmax (mmHg)	PAWPmax (mmHg)	PVRmax (WU)	TPRmax (WU)	COmax (l/min)	mPAP/CO-slope (mmHg/L/min)
18	9	4	2.01	4.47	100	49	18	2.39	3.77	13.00	3.6
18	9	7	2.26	3.99	50	40	29	1.33	4.85	8.24	5.2
13	5	5	1.68	4.75	100	35	24	0.81	2.59	13.5	2.5
14	8	4	2.05	3.61	50	45	34	1.37	5.60	8.04	8.1
18	9	6	1.90	4.74	75	45	23	2.12	4.33	10.40	4.8
17	9	5	2.04	3.93	100	42	18	2.56	4.47	9.39	4.6
12	2	1	2.35	4.25	25	31	-	-	6.11	5.07	23.2*
17	5	4	2.54	5.64	50	27	9	1.65	2.48	10.90	1.9
23	10	8	2.76	4.92	75	50	22	2.85	5.08	9.84	5.5
23	11	4	2.85	4.20	25	44	35	1.42	6.96	6.32	9.9

*Abbreviations: orange: patients with initially suspected EPH or mild PH, red: patients with initially suspected more severe PH, RHC: right heart catheterization, mPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge pressure, RAP: right atrial pressure, PVR: pulmonary vascular resistance, CO: cardiac output, TPR: total pulmonary resistance; *high mPAP/CO slope with very early exercise termination (at 25 Watt level) and only mild increase of cardiac output.*