

Exercise-Induced Pulmonary Hypertension in Scleroderma Patients: A Common Finding but with Elusive Pathophysiology

Rui Baptista, M.D.,*,†, Sara Serra, M.D.,‡, Rui Martins, M.D.,* Maria João Salvador, M.D.,‡ Graça Castro, M.D.,* Manuel Gomes, M.D.,§ Lélita Santos, M.D., Ph.D.,†,§ Pedro Monteiro, M.D., Ph.D.,*,† Jose A. Pereira da Silva, M.D., Ph.D.,†,‡ and Mariano Pêgo, M.D.*

*Department of Cardiology, Coimbra University Hospital, Coimbra, Portugal; †Faculty of Medicine, University of Coimbra, Coimbra, Portugal; ‡Department of Rheumatology, Coimbra University Hospital, Coimbra, Portugal; and §Department of Internal Medicine, Coimbra University Hospital, Coimbra, Portugal

Background: The etiology of exercise-induced pulmonary hypertension (exPH) in systemic sclerosis (SSc) remains a complex task, as both left ventricle (LV) diastolic dysfunction and pulmonary vascular disease can contribute to its development. We determined the incidence of exPH in SSc and examined the association between pulmonary artery systolic pressure (PASP) and tissue Doppler-derived indexes of pulmonary capillary wedge pressure (PCWP). **Methods:** Thirty-eight patients with SSc were studied, using a cycloergometer protocol; 10 were excluded due to resting PH or absence of tricuspid regurgitation (TR); TR and mitral E-wave velocities, LV outflow tract time-velocity integral and LV septal E'-wave were measured before and in peak exercise to calculate cardiac output (CO), PCWP and pulmonary vascular resistance (PVR). **Results:** Mean age of diagnosis was 57.9 ± 8.9 years. At a mean workload of 64 ± 29 Watts, 48% of patients increased $PASP \geq 50$ mmHg. PCWP, assessed by the E/e' ratio, did not change significantly during exercise (10.2 ± 3.1 – 10.0 ± 5.1 ; $P = NS$). Only 3 patients had elevations of the E/e' ratio ≥ 13 during exercise; 2 of them had an exercise $PASP \geq 50$ mmHg, yielding a proportion of exPH due to elevated LV filling pressures of 2/11 (18%). Patients with exPH had lower DL_{CO} and had more frequently the diffuse SSc. **Conclusion:** The elevation of PASP during exercise in most patients of this cohort seems to be related to a reduced pulmonary vascular reserve, and not to an increase in PCWP. Further studies are warranted to determine the therapeutic, as well as prognostic implications of these findings. (Echocardiography 2013;30:378-384)

Key words: pulmonary hypertension, scleroderma, stress echocardiography, diastolic dysfunction

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disorder characterized by widespread vascular lesions and fibrosis of the skin and internal organs.¹ Pulmonary hypertension (PH) is a common complication of SSc associated with a dramatic mortality rate.² Although many patients develop PH as a result of pulmonary arteriopathy (pulmonary arterial hypertension [PAH]), others develop it as a result of pulmonary fibrosis (group 3 PH) or even chronic thromboembolic PH (group 4 PH).³ However, a significant number of patients can develop PH secondary to diastolic dysfunction of the left ventricle (LV), that can lead to an abnormal

increase in pulmonary artery (PA) pressures, due to upstream transmission of associated increase in LV diastolic pressure (pulmonary venous hypertension [PVH], group 2 PH).⁴ The differentiation of these subtypes is critical for the correct management of patients with scleroderma-associated PH, as the prognosis and treatment related to each one of these etiologies is different.⁵

Timely identification of PH and concise characterization of the pathophysiological mechanism involved, especially in its earlier stages, may favorably alter disease management.⁶ As the incidence and severity of PH is highly variable, a tool for early detection and characterization of this complication would be of value for the identification of patients at risk for disease progression.⁷ Current PH guidelines recommend screening SSc patients with an annual resting echocardiogram, as no data firmly supports the use of exercise

Address for correspondence and reprint requests: Rui Baptista, M.D., Department of cardiology, Coimbra University Hospital, Praceta Mota Pinto, 3000 Coimbra, Portugal. Fax: +351-239-400-400; E-mail: ruibaptista@gmail.com

echocardiography.⁵ Besides evaluating tricuspid regurgitation (TR) velocity, a resting echocardiogram can identify subtle alterations in right ventricular (RV) function that may have prognostic impact.^{8,9}

The change in PA systolic pressure (PASP) with exercise provides a possible tool for detection of subclinical pulmonary vascular disease^{4,10,11} and it has been already used for the identification of abnormal pulmonary vascular responses to exercise in patients with a familial predisposition for PAH that is not present at rest.¹² The use of newer noninvasive indicators of LV filling pressures, such as the ratio of mitral E flow-velocity wave and tissue Doppler mitral annulus e' early diastolic velocity (E/e' ratio) during exercise,^{13,14} can help to better characterize the mechanisms of PH in SSc patients. It remains known that in normal subjects, at an average workload of 170 W and cardiac output (CO) of 20 L/min, pulmonary capillary wedge pressure (PCWP), extrapolated by E/e', remains unchanged as compared with resting baseline.¹⁵

We sought to determine the incidence of exercise-induced PH in SSc patients without resting PH. Moreover, we hypothesized that diastolic dysfunction may be associated with a greater increase in PASP during exercise and that this impairment in diastolic function can be identified by echocardiography.

Methods:

The study included, from September 2010 to December 2011, 38 consecutive patients, aged 18 or above, with a rheumatologist or internist-established diagnosis of diffuse or limited SSc according to standard criteria.¹ Patients were referred as part of their routine follow-up care. All patients had normal LV systolic function (ejection fraction >55%) and no echocardiographic evidence of more than mild valvular disease or significant RV dysfunction. Patients were excluded from the study if they presented any of the following criteria: (1) decompensated heart failure on physical examination, (2) absence of TR or if the TR velocity could not be determined accurately, (3) ischemic electrocardiographic changes occurred during exercise, (4) more than mildly elevated PASP at rest (TR velocity gradient superior or equal to 35 mmHg plus estimated right atrial pressure (RAP) of 5 mmHg) when evaluated by continuous-wave Doppler echocardiography, and (5) evidence of more than mild pulmonary disease on recent lung function tests (<1 year old). Patients underwent right heart catheterization (RHC) only if clinically indicated. Protocol was approved by the institutional ethics committee, and all patients gave informed consent.

Study Protocol:

A complete resting echocardiographic examination was performed immediately prior to exercise. Special care was given to determine TR velocity. Evidence (or lack thereof) of congestive heart failure by physical examination was documented prior to exercise. Patients were counseled to exercise until they believed they could go no further and the exercise test was terminated when patients reached their maximum capacity or the maximum expected heart rate. A blood sample was drawn for B-type natriuretic peptide (BNP) sampling, antinuclear antibodies (ANA), anti-centromere antibodies (ACA), and anti-topoisomerase I antibodies (Anti-Scl70). Moreover, 2 quality of life questionnaires were applied: the Stanford Health Assessment Questionnaire (SHAQ), assessing functional capacity, with a score from 0 to 3, the higher the score the higher the impairment; and the Medical Outcomes Study Short Form 36 (MOS SF-36) for assessing quality of life, with a score from 0 to 100, the higher value reflecting the best quality of life.

Stress Doppler Echocardiography:

A standard echocardiographic examination was performed by an experienced operator at rest and during peak exercise. The workload was increased by 25 W every 2 minutes until tolerated or maximal heart rate was attained. Heart rate and blood pressure were recorded at baseline and during the last 30 seconds of each workload. Doppler echocardiography was performed with a Vivid 7 ultrasound system (GE Vingmed Ultrasound, Horten, Norway) on a semi-recumbent cycle ergometer (model 1200 EL; Ergoline, Bitz, Germany). The exercise table was tilted laterally by 20–30° to the left.

Other operator analyzed the offline echocardiographic data. For the assessment of CO, we used the product of estimated from LV outflow tract Cross-sectional area and pulsed Doppler velocity-time integral measurements. Systolic pulmonary artery pressure (PAP) was estimated from a transtricuspid gradient calculated from the maximum velocity (V) of continuous Doppler TR jet, as $4 \times V^2$ plus 5 mmHg assigned to RAP. When needed, contrast was given for more accurate TR velocity assessment. PCWP was estimated from the E/e' ratio, with $PCWP = 1.9 + 1.24 E/e'$. We considered normal PASP values <30 mmHg at rest and <50 mmHg during exercise,¹⁰ whereas an estimated elevation in LV filling pressure during exercise was defined as $E/e' \geq 13$ (corresponding to a PCWP of ≈ 18 mmHg).¹⁴

Statistical Analysis:

Normal distribution was assessed by the Kolmogorov–Smirnov test. If normal distribution

was confirmed values are expressed as mean \pm standard deviation (SD). Otherwise median, 25th and 75th percentiles are given. Significance was tested by Student's *t*-test in case of normal distribution. Otherwise Mann–Whitney–Wilcoxon test was carried out. *P*-values <0.05 were considered statistically significant.

Results:

Feasibility of Exercise Echocardiography in a SSc Population:

We studied a total of 38 SSc patients consecutively presenting to the rheumatology clinic; of these, 23 (71.9%) were enrolled and 10 (31.1%) were excluded (Fig. 1). Eight patients (25.0%) were excluded due to the absence of a good quality TR jet, one to poor compliance to the stress test protocol and one due to the presence of moderate mitral regurgitation. Mean age was 57.9 ± 8.9 years, with a marked female preponderance (22/23; 95.6% females). All patients were in sinus rhythm at the time of stress echocardiography. Mean body mass index was 25.0 ± 3.7 kg/m², mean BNP was 33.7 ± 20.2 pg/dL, and mean DL_{CO} was $95.8 \pm 18.0\%$. All patients were ANA positive, 63.2% were ACA positive and almost one third (31.6%) were Scl70 positive; 20% had diffuse scleroderma form. The mean scores of SHAQ and SF-36 quality of life questionnaires were 0.92 ± 0.53 and 59.8 ± 21.5 , respectively. Data are shown in Table I.

Echocardiographic Data at Rest and Peak Exercise:

Data on exercise echocardiography are shown in Table II. At rest, at a mean heart rate of 71 ± 13 bpm, the mean PASP was 27.5 ± 4.9 mmHg, and mean CO was 4.7 ± 0.9 L/min. Regarding diastolic function, mean E/A was 1.1 ± 0.3 , with a deceleration time of 185 ± 43 msec and mean E/e' was 10.2 ± 3.1 , corresponding to a mean PCWP of 14.0 ± 4.0

mmHg. Pulmonary and PCWP pressures variation with exercise are depicted in Figures 2 and 3. At a mean peak exercise workload of 64 ± 29 Watts, heart rate increased to 112 ± 23 bpm and PASP to 50 ± 11 mmHg, yielding a mean positive variation of 22.2 ± 9.9 mmHg. At peak exercise, CO almost doubled to 9.1 ± 2.2 L/min, an increase of 4.9 ± 2.0 L/min. Regarding LV filling parameters, mean E/A was 1.2 ± 0.4 , with a mean deceleration time of 150 ± 47 msec and a mean E/e' of 10.0 ± 5.1 , corresponding to an estimated PCWP of 14.2 ± 6.3 mmHg.

Changes of PASP and PCWP with Exercise:

Using a PASP ≥ 50 mmHg cutoff, 11 patients (47.8%) were classified as having exercise-induced PH. However, if a 40 mmHg cutoff was used, 20 in 23 (87%) patients would be classified as exercise-induced PH. PCWP, as assessed by the E/e' ratio, did not change significantly during exercise (10.2 ± 3.1 – 10 ± 5.1 , *P* = NS). Only 3 patients had elevations of the E/e' ratio ≥ 13 during exercise. Two of these 3 patients had an exercise PASP over 50 mmHg. The proportion of exercise PH due to elevated PCWP was 2/11 (18%). Figure 3 shows the evolution of echo-derived PCWP during exercise. One patient had a very high exercise-induced elevation in E/e': this patient underwent a RHC with volume loading and was diagnosed as severe diastolic dysfunction.

Discussion:

We studied patients with an established diagnosis of SSc without relevant pulmonary fibrosis or known PAH and demonstrated that exercise-induced PH is a common finding. The elevation in PASP in most patients was not accompanied by a parallel increase in PCWP, as measured by E/e' ratio, suggesting that the main mechanism for exercise-induced PH was low pulmonary vascular reserve.

The occurrence of PH is one of the main clinical problems in SSc and is now the most common cause of scleroderma-related death.¹⁶ The differential diagnosis of PH in SSc is wide, including PAH, PVH, or PH related to lung fibrosis. In a cohort of 599 scleroderma patients, Hachulla et al. demonstrated an prevalence of PAH of 7.9%; interestingly, of the 33 patients identified by resting echocardiography as having suspected PAH, PVH was the cause of PH in 10% of them.¹⁷ In the 3-year follow-up of same cohort, the incidence of PVH was the same as the incidence of PAH (0.61 per 100 patient-years).¹⁸ Therefore, it is crucial to characterize LV filling pressures at rest and during exercise, as an elevated PAP can be caused not only by pulmonary vasculopathy but also by an increase in pulmonary venous pressure, either at rest or during exercise.¹⁹

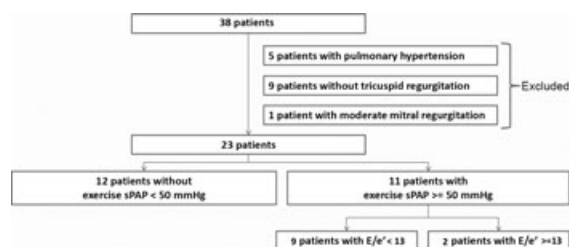


Figure 1. Selection of scleroderma patients for exercise echocardiography. PASP = pulmonary artery systolic pressure; E/e' = ratio of mitral E flow-velocity wave and tissue Doppler mitral annulus e' early diastolic velocity).

TABLE I
Clinical Characteristics of Systemic Sclerosis Patients

Variable	n = 23	Exercise PASP < 50 mmHg (n = 12)	Exercise PASP ≥ 50 mmHg (n = 11)	P-Value
Age (years)	57.9 ± 8.8	57.8 ± 9.2	57.9 ± 8.9	0.984
Female gender (%)	95.7	91.7	100	0.328
Disease duration (years)	11.1 ± 6.5	11.5 ± 6.9	10.5 ± 6.4	0.765
DL _{CO} (% predicted)	95.8 ± 18.0	106 ± 10.8	88.5 ± 19	0.032
BMI (kg/m ²)	25.0 ± 3.7	26.56 ± 3.6	23.6 ± 3.5	0.085
Diffuse form (%)	20	100	0	0.043
Antinuclear antibodies (+) (%)	100	100	100	n/a
Anti-centromere antibodies (+) (%)	63.2	50.0	77.8	0.210
Scl-70 (+) (%)	31.6	50.0	11.1	0.069
Stanford Health Assessment Questionnaire	0.92 ± 0.53	0.91 ± 0.68	0.92 ± 0.38	0.938
Short form-36	59.8 ± 21.5	54.4 ± 17.6	64.1 ± 24.2	0.331
BNP (pg/mL)	33.7 ± 20.2	32.7 ± 18.2	34.7 ± 22.9	0.835

PASP = pulmonary artery systolic pressure.

TABLE II
Echocardiographic Findings at Rest and at Peak Exercise of Systemic Sclerosis Patients

Variable	n = 23	Exercise PASP < 50 mmHg (n = 12)	Exercise PASP ≥ 50 mmHg (n = 11)	P-Value
Workload (Watts)	64.4 ± 28.7	66.7 ± 32.6	61.8 ± 25.2	0.696
Rest HR (per minute)	70.9 ± 12.7	67.9 ± 14.8	74.2 ± 9.7	0.248
Exercise HR, (per minute)	114.7 ± 22.8	110.8 ± 23.5	119 ± 22.2	0.402
Rest PASP (mmHg)	27.6 ± 4.9	24.9 ± 3.7	30.5 ± 4.3	0.003
Exercise PASP (mmHg)	49.9 ± 11	41.7 ± 8	58.8 ± 5.3	0.001
Rest CO	4.6 ± 0.9	3.8 ± 0.6	5.1 ± 0.9	0.037
Exercise CO	9.2 ± 2.1	8.5 ± 2.1	9.9 ± 2.1	0.199
Rest E/e'	10.2 ± 3.1	9.9 ± 2.2	10.5 ± 4	0.659
Exercise E/e'	10 ± 5.1	9.4 ± 2	10.5 ± 7.2	0.605
Rest PCWP (mmHg)	14.6 ± 4	14.3 ± 2.8	15 ± 5.2	0.703
Exercise PCWP (mmHg)	12.1 ± 3.2	11.9 ± 2.2	12.2 ± 4.1	0.850
Rest E/A	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.3	0.388
Exercise E/A	1.2 ± 0.3	1.3 ± 0.4	1.1 ± 0.1	0.190
Rest DT (msec)	186.2 ± 41.6	180 ± 33.6	193 ± 49.7	0.467
Exercise DT (msec)	151 ± 48	140.3 ± 41.9	165.2 ± 54.2	0.248
TAPSE (mm)	22.7 ± 3.1	27.3 ± 5.3	26.8 ± 4.9	0.567

HR = heart rate; PASP = systolic pulmonary artery pressure; mPAP = mean pulmonary artery pressure; CO = cardiac output; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; DT = deceleration time; TAPSE = tricuspid annular plane systolic excursion.

The cause for the inappropriate exercise-induced increase in PAP in patients with SSc is still a matter of debate. In normal subjects, the pulmonary vascular bed is a low-flow, low-resistance system, where an increase in CO, as in exercise, has very little effect on PAP because of the recruitment and distension of pulmonary vessels.²⁰ Interestingly, in SSc target organs, such as the heart, kidneys, or lungs, an abnormality of "vascular reserve" has been demon-

strated in the absence of signs of organ dysfunction.²¹ The loss of the capacity to enhance blood flow upon high request conditions may therefore be present in very early stages of the disease; this concept is supported by pulmonary arterial histology and morphometry analysis, that demonstrates that limited and diffuse SSc patients had a greater area of intima and higher percent luminal occlusion compared with normal controls.²² Moreover,

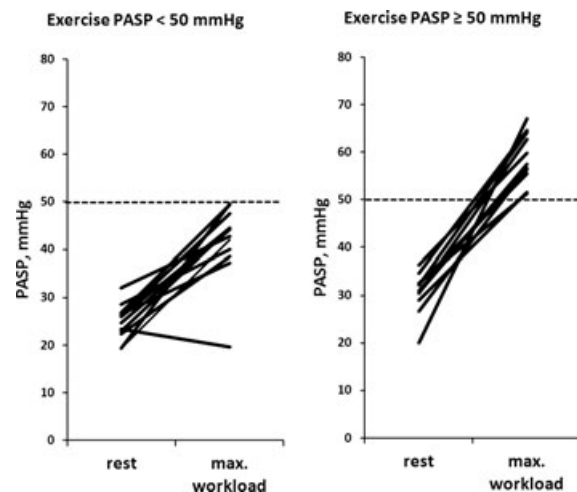


Figure 2. Individual patient-by-patient echo-derived pulmonary artery systolic pressure (PASP).

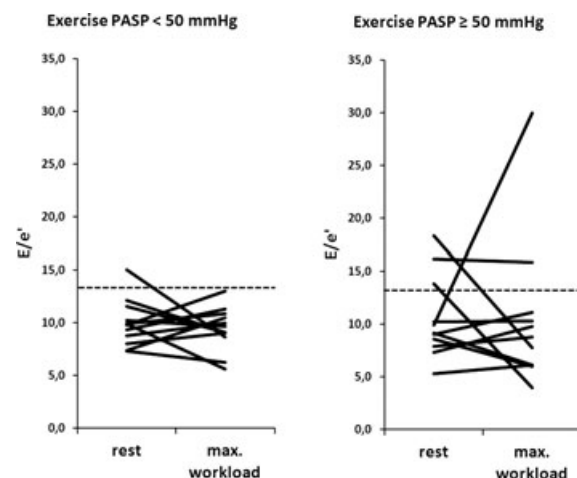


Figure 3. Individual patient-by-patient ratio of mitral E-flow-velocity wave and tissue Doppler mitral annulus e' early diastolic velocity (E/e') at rest and maximum workload. PASP = pulmonary artery systolic pressure.

venular involvement may also be present, sometimes causing veno-occlusive disease.²³

The exercise echocardiogram is a reliable non-invasive technique to detect latent or exercise-induced PH not evident by standard resting Doppler echocardiography.²⁴ In normal subjects, exercise PASP should be <43 mmHg¹²; however, in patients aged 50 years or older, 47% surpassed a pulmonary artery mean pressure (PAMP) of 30 mmHg during maximal exercise.²⁵ Due to very different peak exercise PAP cutoffs, it is difficult to calculate the real prevalence of PH in SSc patients and its clinical relevancy.¹⁹ It is also unclear which of the cutoff values (40, 45, or

50 mmHg of PASP) during exercise is clinically relevant for SSc patients.¹⁹ Up to 60% of SSc patients develop exercise-induced PH when a cutoff of PASP >40 mmHg is used,²⁶ this proportion being independent from age.²⁷ Despite its growing role in the assessment of patients with pulmonary vascular diseases, the use of exercise echocardiogram is not recommended in the latest European PH guidelines due to lack of validation of the PAMP 30 mmHg cutoff.⁵ However, resting and exercise PAMP is correlated with exercise capacity (6 minute walk test and peak VO_2) in SSc patients,²⁸ underlining its potential clinical significance. For the sake of specificity, we considered abnormal a value of exercise PASP over 50 mmHg, as in 2 other studies.^{10,19} In our population, peak exercise PASP was similar to that reported by some,^{27,29} but higher than those reported by other authors.^{11,30–32} Differences in the basal characteristics of the population, exercise protocols and estimated RAP and consequent variations in exercise CO may account for these disparities.

An elevated PAP can be caused not only by pulmonary vascular disease but also by an increase in pulmonary venous pressure due to left heart disease. This stresses the need of accurately estimating LV filling pressures when assessing SSc patients with exercise-induced PH. However, to date, there is no study assessing LV filling pressures during exercise by tissue Doppler echocardiography in SSc patients. The use of E/e' as surrogate marker of PCWP during exercise, the so called diastolic stress test,³³ is based on the fact that in the absence of cardiac disease, e' increases to a similar extent to the increase in mitral E velocity, and the normal E/e' ratio essentially is unchanged with exercise or even reduced,³⁴ paralleling the fact that in normal subjects, the PCWP rarely surpasses 20 mmHg during exercise.³⁵ Conversely, in patients with impaired myocardial relaxation, E/e' increases.¹³ This approach was latter validated by invasive pressure measurements^{14,36} and has significant prognostic impact.^{37,38} We used peak exercise E/e' to determine if SSc patients had significant elevations of LV filling pressures during exercise, therefore accounting for the elevation in PASP. In our population, almost one-fifth of patients who developed exercise-induced PH had an elevation of the E/e' ratio over 13 during peak exercise, corresponding to a PCWP ≥ 18 , the most commonly used cutoff for exercise PVH.^{27,29} Therefore, most patients had normal LV filling pressures at peak exercise, making low pulmonary vascular reserve the most probable cause for elevated PAP during exercise in the majority of cases. The proportion of patients with PH due to LV disease in our cohort was similar to that

reported to Steen et al. (13%).²⁹ Two other recent studies found a higher proportion (38% and 75%) of PVH among SSc patients.^{19,30} D'Alto et al.³¹ also highlighted the association of subtle LV dysfunction with a greater increase in PASP with exercise in a recent study, using e'/a' as a marker of resting LV diastolic dysfunction. Undoubtedly, a systematic follow-up of these patients is warranted, to determine if the elevation of PH during exercise is associated with a higher incidence of resting PH.

Patients with SSc with no signs of PH at rest but with exertion dyspnea might undergo exercise echocardiography as part of their assessment, to uncover the mechanism of exercise limitation. If significant exercise-induced PH is detected, a closer follow-up of these patients may be warranted and a program of exercise training may be implemented.³⁹ To date, there is no evidence supporting the use of selective pulmonary vasodilators in this group of patients.⁵

Study Limitations:

Our study has some acknowledged limitations, being a single-center study with a small sample size. As RHC was not performed in all patients, the intracavitary pressure values are derived from echocardiography. However, one of the patients that had a very significant elevation of E/e' was later catheterized, confirming the elevation in LV filling pressures even at rest.

Conclusion:

In our study, exercise-induced PH was very common in patients with SSc, even when resting PASP was normal. The elevation of PASP during exercise in most patients of this cohort seems to be related to a reduced pulmonary vascular reserve, and not to an increase in PCWP. Further studies are warranted to determine the therapeutic, as well as prognostic implications of these findings.

Acknowledgements: We would thank António Duarte and Liliانا Alves for technical support and Sónia Cancela for logistics.

References

- Masi AT: 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;23:581–590.
- Hachulla E, Carpentier P, Gressin V, et al: Risk factors for death and the 3 year survival of patients with systemic sclerosis: The French ItinAIR Sclérodémie study. *Rheumatology (Oxford)* 2009;48:304–308.
- Vachiéry J-L, Coghlan G: Screening for pulmonary arterial hypertension in systemic sclerosis. *Eur Respir Rev* 2009;18:162–169.
- Huez S, Roufosse F, Vachiéry J-L, et al: Isolated right ventricular dysfunction in systemic sclerosis: Latent pulmonary hypertension? *Eur Respir J* 2007;30:928–936.
- Galiè N, Hoeper MM, Humbert M, et al: Guidelines for the diagnosis and treatment of pulmonary hypertension: The 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 the Internat. *Eur Heart J* 2009;30:2493–2537.
- Galiè N, Rubin L, Hoeper M, et al: Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): A double blind, randomised controlled trial. *Lancet* 2008;371:2093–2100.
- Condliffe R, Kiely DG, Gibbs JSR, et al: Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension. *Am J Respir Crit Care Med* 2008;177:1122–1127.
- Ivanovic BA, Tadic MV, Zlatanovic MM, et al: Which factors impact myocardial function in systemic sclerosis? *Echocardiography* 2012;29:307–317.
- Frea S, Capriolo M, Marra WG, et al: Echo Doppler predictors of pulmonary artery hypertension in patients with systemic sclerosis. *Echocardiography* 2011;28:860–869.
- Callejas-Rubio JL, Moreno-Escobar E, de la Fuente PM, et al: Prevalence of exercise pulmonary arterial hypertension in scleroderma. *J Rheumatol* 2008;35:1812–1816.
- Alkottob ML, Soltani P, Sheatt MA, et al: Reduced exercise capacity and stress induced pulmonary hypertension in patients with scleroderma. *Chest* 2006;130:176–181.
- Grünig E, Weissmann S, Ehlken N, et al: Stress Doppler echocardiography in relatives of patients with idiopathic and familial pulmonary arterial hypertension: Results of a multicenter European analysis of pulmonary artery pressure response to exercise and hypoxia. *Circulation* 2009;119:1747–1757.
- Ha J-W, Oh JK, Pellikka PA, et al: Diastolic stress echocardiography: A novel noninvasive diagnostic test for diastolic dysfunction using supine bicycle exercise Doppler echocardiography. *J Am Soc Echocardiogr* 2005;18:63–68.
- Burgess MI, Jenkins C, Sharman JE, Marwick TH: Diastolic stress echocardiography: Hemodynamic validation and clinical significance of estimation of ventricular filling pressure with exercise. *J Am Coll Cardiol* 2006;47:1891–1900.
- Argiento P, Chesler N, Mulè M, et al: Exercise stress echocardiography for the study of the pulmonary circulation. *Eur Respir J* 2010;35:1273–1278.
- Steen VD, Medsger TA: Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis* 2007;66:940–944.
- Hachulla E, Coghlan JG: A new era in the management of pulmonary arterial hypertension related to scleroderma: Endothelin receptor antagonism. *Ann Rheum Dis* 2004;63:1009–1014.
- Hachulla E, deGroot P, Gressin V, et al: The three year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. *Arthritis Rheum* 2009;60:1831–1839.
- Kovacs G, Maier R, Aberer E, et al: Assessment of pulmonary arterial pressure during exercise in collagen vascular disease: Echocardiography vs right sided heart catheterization. *Chest* 2010;138:270–278.
- Raese DA, Brown A, Patel KR, et al: Ambulatory pulmonary artery pressure monitoring during sleep and exercise in normal individuals and patients with COPD. *Thorax* 2002;57:1050–1053.
- Pignone A, Mori F, Pieri F, et al: Exercise Doppler echocardiography identifies preclinical asymptomatic pulmonary hypertension in systemic sclerosis. *Ann N Y Acad Sci* 2007;1108:291–304.

22. al-Sabbagh MR, Steen VD, Zee BC, et al: Pulmonary arterial histology and morphometry in systemic sclerosis: A case control autopsy study. *J Rheumatol* 1989;16:1038–1042.
23. Dorfmueller P, Humbert M, Perros F, et al: Fibrous remodeling of the pulmonary venous system in pulmonary arterial hypertension associated with connective tissue diseases. *Hum Pathol* 2007;38:893–902.
24. Vachier J-L, Pavelescu A: Exercise echocardiography in pulmonary hypertension. *Eur Heart J Suppl* 2007;9:H48–H53.
25. 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;34:888–894.
26. Lau EMT, Manes A, Celermajer DS, Galiè N: Early detection of pulmonary vascular disease in pulmonary arterial hypertension: Time to move forward. *Eur Heart J* 2011;32:2489–2498.
27. Saggar R, Khanna D, Furst DE, et al: Exercise induced pulmonary hypertension associated with systemic sclerosis: Four distinct entities. *Arthritis Rheum* 2010;62:3741–3750.
28. Kovacs G, Maier R, Aberer E, et al: Borderline pulmonary arterial pressure is associated with decreased exercise capacity in scleroderma. *Am J Respir Crit Care Med* 2009;180:881–886.
29. Steen V, Chou M, Shanmugam V, et al: Exercise induced pulmonary arterial hypertension in patients with systemic sclerosis. *Chest* 2008;134:146–151.
30. Ciurzyński M, Bienias P, Irzyk K, et al: Usefulness of echocardiography in the identification of an excessive increase in pulmonary arterial pressure in patients with systemic sclerosis. *Kardiol Pol* 2011;69:9–15.
31. D'Alto M, Ghio S, D'Andrea A, et al: Inappropriate exercise induced increase in pulmonary artery pressure in patients with systemic sclerosis. *Heart* 2011;97:112–117.
32. Collins N, Bastian B, Quiquere L, et al: Abnormal pulmonary vascular responses in patients registered with a systemic autoimmunity database: pulmonary Hypertension Assessment and Screening Evaluation using stress echocardiography (PHASE I). *Eur J Echocardiogr* 2006;7:439–446.
33. Oh JK, Park S-J, Nagueh SF: Established and novel clinical applications of diastolic function assessment by echocardiography. *Circ Cardiovasc Imaging* 2011;4:444–455.
34. Ha JW, Lulic F, Bailey KR, et al: Effects of treadmill exercise on mitral inflow and annular velocities in healthy adults. *Am J Cardiol* 2003;91:114–115.
35. Ehram RE, Perruchoud A, Oberholzer M, et al: Influence of age on pulmonary haemodynamics at rest and during supine exercise. *Clin Sci (Lond)* 1983;65:653–660.
36. Talreja DR, Nishimura RA, Oh JK: Estimation of left ventricular filling pressure with exercise by Doppler echocardiography in patients with normal systolic function: A simultaneous echocardiographic cardiac catheterization study. *J Am Soc Echocardiogr* 2007;20:477–479.
37. Shim CY, Kim S-A, Choi D, et al: Clinical outcomes of exercise induced pulmonary hypertension in subjects with preserved left ventricular ejection fraction: Implication of an increase in left ventricular filling pressure during exercise. *Heart* 2011;97:1417–1424.
38. Holland DJ, Prasad SB, Marwick TH: Prognostic implications of left ventricular filling pressure with exercise. *Circ Cardiovasc Imaging* 2010;3:149–156.
39. Mereles D, Ehlken N, Kreuscher S, et al: Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation* 2006;114:1482–1489.