Six-minute walk test reflects neurohormonal activation and right ventricular function in systemic sclerosis patients

K. Irzyk[1], P. Bienias[1], M. Kostrubiec[1], Z. Rymarczyk[1], Z. Bartoszewicz[2,3], M. Siwicka[4], A. Stelmaszczyk-Emmel[5], E. Górska[5], U. Demkow[5], P. Pruszczyk[1], M. Ciurzyński[1]

[1]Department of Internal Medicine and Cardiology, and [2]Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw; [3]Department of Endocrinology, Warsaw Medical Research Centre of Polish Academy of Science, Warsaw; [4]Department of Dermatology, and [5]Department of Laboratory Diagnostics and Clinical Immunology of Developmental Age, Medical University of Warsaw, Warsaw.

Katarzyna Irzyk, MD
Piotr Bienias MD, PhD
Maciej Kostrubiec, MD, PhD
Zuzanna Rymarczyk, MD
Zbigniew Bartoszewicz, MD. PhD
Maria Siwicka MD, PhD
Anna Stelmaszczyk-Emmel, MD, PhD
Elżbieta Górska, MD, PhD, Eng
Urszula Demkow, MD, PhD
Piotr Pruszczyk, MD, PhD, FESC
Michał Ciurzyński, MD, PhD

Please address correspondence to:
Dr Katarzyna Irzyk,
Department of Internal Medicine and Cardiology,
Medical University of Warsaw,
Lindleya 4,
02-005 Warsaw, Poland.
E-mail: kirzyk35575@gmail.com

Received on May 17, 2012; accepted in revised form on September 26, 2012.

Clin Exp Rheumatol 2013; 31 (Suppl. 76): S18-S23.

Key words: connective tissue diseases, scleroderma, six-minute walk test, echocardiography, neurohormones

Funding: this study was supported by the KBN N402 085034 grant.

Competing interests: none declared.

ABSTRACT

Objective. *Heart and pulmonary involvement is a leading cause of systemic sclerosis (SSc)-related deaths. The six-minute walk test (6MWT) is a simple and reproducible test commonly used to evaluate exercise capacity. We tried to assess a potential relationship between exercise capacity assessed by 6MWT, echocardiographic parameters of right ventricular function and serum levels of endothelin-1 and NTproBNP.*

Methods. *We prospectively studied 111 consecutive patients (101F, 10M, age 54.2±13.8 years) with diagnosed SSc (mean disease duration 9±12.4 years) and a group of 21 age-matched subjects (18F, 3M, age 49.3±10.5 years). In addition to routine evaluation, 6MWT and transthoracic echocardiography (Phillips iE 33) were performed. We also measured serum endothelin- 1 (Human Endothelin-1 immunoassay R&D Systems) and NT-proBNP levels (Elecsys pro-BNP immunoassay; Roche Diagnostics).*

Results. *The mean 6MWT distance was significantly shorter in the SSc group than in the controls (562.8±60.3 vs. 514.7±102.5 m, p=0.03). In the SSc group 6MWT distance correlated with ET-1 (r=-0.5, p<0.0001), NT-proBNP (r=-0.4, p=0.0008) levels, and echocardiographic indices AcT (r=0.4, p=0.0002) and TRPG (r=-0,4, p=0.0011). Moreover, in patients with 6MWT distance <450 m NTproBNP and endotothelin- 1 levels were significantly higher than in patients with distance >450 m (311.2, 31.1–17237 vs. 105.3, 5–17670 pg/ml, p=0.0138 and 2.9±2.2 vs. 1.4±0.7 pg/ml, p=0.0032).*

Conclusions. *Decreased exercise capacity significantly correlates with biochemical and echocardiographic parameters of right ventricular dysfunction and neurohormonal activation providing a potential link for neuroendocrine derangement in patients with SSc.*

Introduction

Pulmonary hypertension (PH) and interstitial lung disease (ILD) are the leading causes of SSc-related deaths (1). Unfortunately, when the PH symptoms appear, the disease is usually in an advanced stage and it is very difficult to influence its progress. Defining non-invasive diagnostic modalities, which may help to detect patients with SSc in an early stage of pulmonary vasculature involvement, is of important clinical value and therefore is an attractive topic of clinical research.

The six-minute walk test (6MWT) is an easy and available test. Results of the 6MWT, especially the distance achieved during the test are regarded as a measure of a patient's real exercise capacity. Furthermore, 6MWT when performed in regular time intervals can be also used for assessment of the disease progression and estimate therapy results.

Echocardiography may detect both systolic and diastolic impairment of left and right ventricle (LV, RV) and RV overload. Transthoracic echocardiography is a non-invasive screening test in the diagnosis of PH, and is used to monitor disease progression in patients with already diagnosed PH (2) Serum levels of endothelin-1 (ET- 1), a strong vasoconstrictor and pro-mitotic peptide are increased in patients with pulmonary arterial hypertension (PAH) (3), while levels of NT-proBNP a marker of ventricular stress, can reflect both ventricular dysfunction and the severity of their overload (4). It is also known, that NT-proBNP has a significant prognostic value in PAH (5). We tried to evaluate potential relationship between exercise capacity assessed by 6MWT, echocardiographic parameters

of RV function and serum levels of ET-1 and NT-proBNP, indices of neurohormonal activation.

Materials and methods

Patients

One hundred and eleven consecutive patients (101 women, 10 men, mean age 54.2±13.7 years) with systemic sclerosis as defined by the American College of Rheumatology criteria, mean time 9.4±11 years from diagnosis, were included in to this study (6). Exclusion criteria consisted of documented angina and history of myocardial infarction, paroxysmal and permanent atrial fibrillation, cardiac pacing, significant valvular heart disease, LV hypertrophy (LV walls ≥11 mm assessed by echocardiography) and impaired renal function (GFR<15 ml/min/1.73m^2). Creatinine clearance was calculated by Modification of Diet in Renal Disease Study Group (MDRD) formula. Moderate Chronic Obstructive Pulmonary Disease (COPD) defined according to the GOLD criteria FEV1%FVC <0.7 (70%) and FEV1 <80% predicted disqualify from the study (7). As a control group we assessed 21 age and sex–matched subjects (18 females, 3 males, mean age 49.3±10.5 years). Special attention was taken to select the control group with the same profile of coexisting systemic hypertension and treated with the hypotensive therapy as used in the study group. These subjects had no data for pulmonary diseases and presented no echocardiographic evidence of structural heart disease. The exclusion criteria were the same as for study group.

All patient gave written consent. The study was accepted by the Local Bioethic Committee (Medical University of Warsaw Ethics Committee, no. KB66/2006).

Clinical characteristics

Rodnan score was used to evaluate the progression of SSc (8). In all patients high resolution computed tomography HRCT (Toshiba Aquilion 64), chest radiography (Siemens Eidos RF 439, Mecall, Italy), pulmonary function testing and measurement of single breath diffusing lung capacity for carbon monoxide DLCO (Vmax 229 SensorMedics, Yorba Linda, USA) were performed in order to evaluate the pulmonary involvement.

Serological parameters

All patients were screened for the presence of autoantibodies. The following serological markers were analysed: anti-nucleolar antibody (ANA), and anti-centromere antibody (ACA) by indirect immunofluorescence on monkey esophagus at a dilution of the serum of 1:20 and on Hep 2 cell line at a dilution of 1:40. Anti-extractable nuclear antigen (ENA) antibodies, including Scl-70 antibodies, were identified by double immunodiffusion.

Biochemical assays

Fasting blood samples were taken from an antecubital vein. Blood samples for NT- pro BNP and ET-1 determinations were centrifuged and frozen (-75 C degrees) until assayed. ET-1 was measured with QuantiGlo Human Endothelin-1 immunoassay Cat. No QET00B (R&D Systems, Inc. Minneapolis, MN, USA) according to manufacturer's protocol. Fluoroskan Ascent FL microplate luminometer (Thermo Labsystems Oy Helsinki, Finland) was used to measure the intensity of the light emitted and Ascent Software, v. 2.6 was used for creation of standard curves, curve fitting and calculation of concentrations. The concentration of NT-proBNP was analysed on Elecsys 2010 automatic analyser (Roche Diagnostics Gmbh). Serum NT-proBNP concentration higher than 125 pg/ml was regarded as abnormal as indicated by the producer.

Six-minute walk test

The 6MWT was performed on a level hallway surface. Ten minutes before the test, while patient was resting, he was given a standardised instruction and asked to grade his shortness of breath by using Borg's scale (9). Immediately prior to the test, the patient's blood pressure and heart rate were examined. By finger probe pulse oximeter ("Oxy Shuttle 2", Criticon) oxygen blood saturation (SpO2) was measured. During the test the patient was not given any instructions or encouragement. When he stopped during the test we did not pause the time. The test was stopped in case of pain in the chest, significant dyspnea, leg cramps, staggering, diaphoresis and if the patient requested it. Immediately after the test all before-mentioned parameters were again examined. According to the American Thoracic Society (ATS) Guidelines we did not monitor SpO2 during the test (10). According to a previous study we chose the distance 450 meters as the borderline between normal and impaired and then we analysed parameters in both groups (11). Desaturation (ΔSpO2) was defined as a difference between the baseline blood saturation and SpO2 measured immediately after the test.

Echocardiography

Echocardiographic studies were performed with Phillips iE33 system (Andover, Md., USA) with 2.5–3.5 MHz transducers. Patients were examined in the left lateral position.

After recording the tricuspid valve peak systolic velocity with continuous-wave Doppler echocardiography, the tricuspid regurgitation peak gradient (TRPG) was calculated according to the simplified Bernoulli equation. The pulmonary hypertension was suspected as a TRPG >31 mmHg (tricuspid regurgitant velocity >2.8 m/s) (2). Acceleration time of pulmonary ejection (AcT) was measured using pulse wave Doppler with sample volume placed in the RV outflow tract just below the pulmonary valve. Measurements were averaged over 5 consecutive heart cycles. The Tei index for the right ventricle was calculated by dividing the sum of RV isovolumetric contraction and relaxation time by RV ejection time, described previously (12). The LV ejection fraction (EF%) was calculated according to the modified Simpson rule using apical four- and two-chamber views.

Analysis of LV diastolic performance

To evaluate the left ventricle diastolic function we measured the E/A and E/E' parameters in SSc and control group.

Mitral valve inflow (MVF) was recorded in the apical four-chamber view

with Doppler gate positioned in the LV on the level of the mitral valve edges. The following parameters were evaluated: peak velocity of the early inflow phase (E), peak velocity of the atrial inflow phase (A) and E/A ratio.

Tissue Doppler mitral annular early diastolic velocities

Tissue Doppler imaging (DTI) was performed in the apical views to acquire mitral annular velocities. The sample volume was positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5–10 mm) to cover the longitudinal excursion of the mitral annulus in diastole.

Lateral annulus early diastolic velocity (Mit E' lateral) was measured. Mitral E/E' lateral was also calculated.

Statistical analysis

Data characterised by a normal distribution are expressed as a mean followed by a standard deviation. Parameters without such distribution are expressed as a median with a range. Patients with SSc and controls were compared with Wilcoxon test depending on the character of parameters distribution. For categorical variables, the differences between the groups were compared with Chi-squared test or Fisher's exact test. Correlations between 6MWD and echocardiographic and biochemical variables were evaluated by Spearman's correlation coefficients. Univariate analysis of variance was performed to detect predictors of distance <450 meters in the SSc group. Receiver-operating characteristic (ROC) analysis were performed for the selection for the optimal cut off value of the NT-proBNP and ET-1 levels for the prediction of 6MWT distance <450 m. ROC analysis was performed in order to define the optimal 6MWT distance for TRPG >31 mmHg detection. An analysis was performed using a statistical software package (SAS 9.2). $p<0.05$ was considered statistically significant.

Results

Finally our study included 111 SSc patients and 21 age-matched volunteers. Clinical features of the SSc group are given in Table I. and the general characteristics of the study population is included in Table II.

Table I. Clinical features of the SSc group.

Parameters	Mean	No.	%
Disease duration (years)	9.4 ± 11		
Diffuse scleroderma		40	36
Limited scleroderma		57	51
Type unknown		14	13
Rodnan score (points)	6.4 ± 6.7		
ANA positive		105	95
ACA positive		34	31
Anti Scl 70 positive		56	50
VC % predicted	2.9 ± 0.8		
FVC % predicted	100.4 ± 18.3		
FEV1% predicted	94.7 ± 19.7		
FEV/FVC % predicted	79.7 ± 8.2		
DLCO % predicted	70.7 ± 19		

ACA: anticentromere antibodies; ANA: antinuclear antibodies; VC: vital capacity; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; DLCO: lung diffusing capacity for carbon monoxide.

Table II. General characteristics of the study population.

Parameters	SSc patients (n=111)	Control group (n=21)	*p*-value
Men	10 (9%)	3 (14%)	ns
Women	101 (91%)	18 (86%)	ns
Age (years)	54.2 ± 13.7	49.3 ± 10.5	ns
BSA (m^2)	1.73 ± 0.3	1.72 ± 0.2	ns
Systemic hypertension	37 (33%)	6 (29%)	ns

BSA: body surface area.

Treatment

Angiotensin-converting enzyme inhibitors (ACE-I) received 31(28%) SSc patients, angiotensin II receptor antagonists: 7(6%), beta adrenolytics: 10(9%), diuretics: 16(14%), calcium channel blockers: 27(24 %). Due to the progression of SSc 15 (13.5%) patients received immunosupressant agents (glucocorticoids and cyclophosphamide). We did not find statistically significant differences in the use of cardiovascular medication between the SSc and control group.

6MWT, biochemical and echocardiographic parameters

The 6MWT, biochemical and echocardiographic results are presented in Table III.

The 6MWT was performed in 93 patients. In 10 patients skin lesions of the distal parts of fingers made it impossible to reliably measure oxygen saturation which resulted the exclusion of these patients from further analysis. In 8 SSc patients we did not perform 6MWT due to orthopaedic conditions preventing them from undergoing an adequate physical exercise. The mean 6MWT distance was significantly shorter in the SSc group than in the controls. In the SSc patients the mean saturation of capillary blood before and after 6MWT was lower than in the controls. Moreover, the mean desaturation after test (Δ sat) was significantly more pronounced in the SSc group than in controls.

The mean NT- pro-BNP serum concentration was over the normal level indicated by the producer (>125 pg/ml) in 50 (45%) of the SSc patients but in none of the control group. The median level of NT-proBNP and mean of ET-1 was significantly higher in the SSc patients than in the controls. As far as echocardiographic parameters are concerned, although the mean TRPG value was ≤31 mmHg in both groups, it was significantly higher in the SSc patients than in the controls. Interestingly, the TRPG >31 mmHg was found in 22 (24%) SSc patients and in none of the patients from the control group.

AcT was significantly shorter in the SSc group than in controls. Moreover, mean RV Tei index was increased in comparison to the control group. We found an incorrect RV Tei index (>0.4) in 29 (26%) SSc patients.

Significant correlations between 6MWD and biochemical and echocardiographic parameters are summarised in Table IV.

To evaluate the LV diastolic function we measured the E/A and E/E' parameters in the SSc and control group. We did not find significant correlations between left ventricle diastolic dysfunction parameters and 6MWT distance.

Predictors of distance <450m

According to the distance achieved during the 6MWT, we divided the SSc patients into two groups: <450 m and ≥450 m. The results are shown in Table V.

Higher mean ET-1 and median NT-proBNP serum concentration was found in a group with shorter 6MWD.

Echocardiography showed that the mean value of AcT was significantly shorter in the <450m group than in the remaining patients (108 *vs*. 121 ms, *p*=0.018). The mean values of TRPG and RV Tei index tended to be higher in the former, however, the difference did not reach significance (28.4 *vs*. 25.7 mmHg, NS and 0.38 *vs*. 0.3, NS).

Using univariate analysis we found, that a decrease of 1 ms of AcT and increase in 0.1 pg/ml of ET-1 predicted the distance <450m (Table VI).

ROC analysis was performed in order to define the optimal serum ET-1 level for 6MWT distance <450m detection.

The area under the curve (AUC) was 0.7333. A cut-off value of 1.82 pg/ml showed 80% sensitivity, 68% specificity, positive predictive value (PPV) of 89% and negative predictive value (NPV) of 52% for 6MWT distance <450 m.

In order to define the optimal serum NT-proBNP level for 6MWT distance <450m detection ROC analysis was performed.

The area under the curve (AUC) was 0.6917. A cut-off value of 311 pg/ml showed 92% sensitivity, 53% specificity, positive predictive value (PPV) of 87% and negative predictive value (NPV) of 67% for 6MWT distance <450m.

ROC analysis was performed in order to define the optimal 6MWT distance for TRPG >31 mmHg detection.

The area under the curve (AUC) was 0.7697. A cut-off value of 483m showed 77% sensitivity, 55% specificity, positive predictive value (PPV) of 86% and negative predictive value (NPV) of 42% for TRPG >31 mmHg.

Table III. SixMWT, biochemical and echocardiographic results.

Parameters	Ssc (n=111)	Controls (n=21)	*p*-value
Distance (m) (n=93)	514.7 ± 102.5	562.8 ± 60.3	0.03
SO2_1 (%) (n=93)	95.7 ± 4.7	97.6 ± 1.1	0.03
SO2_2 (%) (n=93)	93.2 ± 6	96.7 ± 2.1	0.01
ΔSO2 (%) (n=93)	3.0 ± 4.7	0.9 ± 2.7	0.01
NT- pro BNP (pg/ml) (n=111)	133.5 (5- 17670)	62.2 (30.8- 116.4)	0.0002
Endothelin- 1 (pg/ml) (n=111)	1.9 ± 1.4	1.3 ± 0.6	0.002
TRPG (mmHg) (n=111)	26.7 ± 7	17.8 ± 4.1	<0.0001
RV Tei index (n=102)	0.4 ± 1	0.3 ± 0.02	< 0.0001
AcT (ms) (n=111)	116.5 ± 21.1	134.7 ± 16	0.0006
Mitral E/A (n=111)	0.98 ± 0.3	1.21 ± 0.28	0.002
E/E' (n=111)	10.87 ± 3.82	6.87 ± 2.30	ns

SO2_1: blood oxygen saturation before 6MWT; SO2_2: blood oxygen saturation after 6 MWT; ΔSO2: desaturation, NT-proBNP: N-terminal pro-B type natriuretic peptide; TRPG: tricuspid regurgitant peak gradient; AcT: acceleration time.

Table IV. Significant correlations between 6MWT distance and biochemical and echocardiographical parameters.

Parameters	r	*p*-value
Endothelin-1 (pg/ml)	-0.47	<0.0001
NT- proBNP (pg/ml)	-0.36	0.0008
AcT	0.37	0.0002
TRPG	-0.36	0.0011

NT-proBNP: N-terminal pro-B type natriuretic peptide; TRPG: tricuspid regurgitant peak gradient; AcT: acceleration time of pulmonary ejection.

Table V. Biochemical and clinical features of patients with the 6MWD<450 m and ≥450 m.

Parameters	<450 m (n= 20)	≥450 m (n= 73)	*p*-value
Age (years)	61.1 ± 10.2	50.6 ± 12.8	0.0019
SO2_1 (%)	93.2 ± 6.8	96.2 ± 3.8	0.0088
NT- proBNP (pg/ml)	311.2 (31.1-17237)	105.3 (5-17670)	0.0138
Endothelin-1 (pg/ml)	2.9 ± 2.2	1.4 ± 0.7	0.0032

SO2_1: blood oxygen saturation before 6 MWT; NT: proBNP: N-terminal pro-B type natriuretic peptide.

Table VI. Univariate predictors of the distance <450 m.

Parameter	OR	95% CI	*p*-value
Endothelin-1 – increase of 0.1 pg/ml	1.095	1.031 – 1.163	0.0033
AcT – decrease of 1 ms	1.033	1.006 – 1.060	0.0165

AcT: acceleration time of pulmonary ejection.

Discussion

The six-minute walk test is a simple and easily available inexpensive diagnostic tool widely used for exercise capacity evaluation. However, this test does not provide any specific information about the disease. It presents only the global physical capacity, and is related to cardiopulmonary and musculoskeletal function. Six MWT is recommended for prognostic evaluation in

PAH patients, because it is a strong and independent mortality predictor and correlates with the NYHA/WHO classification (13, 14). Moreover, 6MWT can be widely used to evaluate the results of therapy. Assessment of the SSc-related PAH patients is difficult (15). Six MWT was reported to reflect cardiopulmonary complications in SSc (16-18). In our study patients with SSc had statistically significant shorter 6-minute walk distance (6MWD) than the control group (p=0.03) which is in accordance with previous studies (19, 20). We also evaluated blood oxygen saturation before and after the 6MWT and we found that SpO2 before and after 6MWT was significantly lower in the SSc patients. In contrast to our observation, Huez *et al*. found no differences between the SpO2 in SSc patients and controls neither before nor after the test (20). Moreover, in our study mean desaturation was significantly, more pronounced in SSc patients. Villalba *et al*. in a group of 110 SSc patients revealed that Δ sat <4% was associated with 6MWT <400 m (21).

Only a few studies previously reported elevated ET-1 levels in SSc patients (22- 24). In our study, serum ET-1 level was increased when compared to the control group. These findings support the hypothesis of vascular dysfunction in patients with SSc. Interestingly, NT-proBNP serum concentration was also higher in our SSc group than in controls which may reflect RV overload.

We have found a significant negative correlation between the 6MWD and serum NT-proBNP level. Other studies in patients with SSc also found similar correlations (19, 25). However, coexisting significant negative correlation of ET-1 with 6MWD suggest that distance achieved during the 6MWT reflects neurohormonal activation in the SSc patients group. As far as we know, there are no studies in which a correlation between the 6MWD and ET- 1 was found in SSc patients.

ESC guidelines for the treatment and diagnosis of PH recommend yearly echocardiography in symptomatic patients with SSc and suggest this screening examination even in asymptomatic cases (2). According to these guidelines, tricuspid regurgitant peak gradient (TRPG) >31 mmHg may indirectly suggest PH. In our study we also evaluated TRPG the mean value of which was significantly higher in the SSc patients than in the control group. As a marker of RV function impairment we used RV Tei index. Recent guidelines for the echocardiographic assessment of right heart in adults emphasised that the RV Tei index is a useful parameter which allow global estimation of both systolic and diastolic function of RV (26). Moreover, we found shorter AcT in the SSc patients than in controls suggesting disturbed coupling to the pulmonary arterial bed. In our study 6MWD correlated negatively with TRPG and positively with AcT. These results implicate the usefulness of 6MWT in indirect assessment of RV function and pulmonary circulation condition.

Deushle *et al*. analysed 101 patients with SSc and found that 6MWD 473m is the best value to identify patients with PAH (27). Degano *et al*. analysed 49 consecutive patients with PAH walking more than 450m in 6MWT. They found that antropometric characteristics, including younger age, lower BMI and greater height in these patients may explain longer 6MWD. It is important to emphasise, that distance ≥450 m is regarded as "near normal" and patients with such 6MWD are usually excluded from randomised clinical trials, while they still can suffer from a severe haemodynamic impairment. Degano *et al*. suggested that patients with longer distance may benefit from PAH specific treatment (11). That is why we chose the distance 450 meters as the borderline between normal and impaired value and then we analysed the parameters in both groups. There was no statistically significant antropometric differences (BSA) between these two groups, although patients with 6MWD >450m were younger. They also had higher baseline blood oxygen saturation and lower NT-proBNP and ET-1 serum concentration level. Schmidt *et al*. examined 63 SSc patients. The subjects with PAH had a higher ET-1 plasma concentration level than without PAH. The cut-off value for ET-1 plasma level to discriminate patients affected by PAH was 4.1 pmol/l (1.1 pg/ml) (28). In our study, the ET-1 plasma level 1.82 pg/ml is the best cut-off value to predict the distance <450m. Furthermore, we determined the cut-off value 311 pg/ml for serum NT-pro BNP level to predict this shorter distance. Chighizola *et al*. found that NT- proBNP was significantly increased in SSc patients with heart involvement. They have also found that NT-proBNP level of 50 pmol/L predict the presence of cardiac involvement in SSc with a sensitivity of 90.5% and specificity of 97.6% (29). Williams *et al*. noticed a significant correlation between the distance <350m and NT-proBNP serum level (r=-0.46, p<0.0001). In their study the cut off value of NT-proBNP >396 pg/ml strongly supports the diagnosis of SSc PAH (25).

There are a lot of evidence that LV diastolic function is impaired in SSc patients (30, 31). Recently, Hinchcliff *et al*. have found that left ventricle diastolic dysfunction is a marker of increased risk of death (32). In our study, parameters of left ventricle diastolic function were impaired in the SSc patients but E/E' and E/A were not correlated with the 6MWD.

Limitations of the study

In our study we did not estimate precisely indices of lung function and their potential impact on the physical, echocardiographic and biochemical parameters. However, to minimise a potential influence we excluded patients with impaired results of spirometry.

Clinical implication

Our study shows, that 6MWT may be used as an indirect tool for estimation of pulmonary vascular and RV impairment. When performed regularly, 6MWT may allow early detection of cardiopulmonary complications in SSc. We determined the optimal 6MWD to predict elevated TRPG. In our opinion the distance below 483 m, not as previously reported below 400–300 meters, can be used for indentification of patients with a worse prognosis. Therefore, we should focus our attention

on SSc patients who achieve 6MWD <450 m. Moreover, we discriminated optimal serum ET- 1 and NT-proBNP concentration levels that can predict the distance <450 m. Biomarkers can also be a useful tool in evaluating physical capacity and, indirectly, disease progression, especially in patients who may not be able to perform 6MWT.

Conclusions

Our study showed a potential link between the decreased physical capacity and the vascular and heart dysfunction in SSc patients. Six-MWD reflects neurohormonal activation and RV impairment and as a simple and inexpensive diagnostic tool it can be used in the assessment of heart and pulmonary function.

References

1. STEEN V: Advancements in diagnosis of pulmonary arterial hypertension in scleroderma. *Arthritis Rheum* 2005; 52: 3698-700.
2. GALIE 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 International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493-537.
3. MAYES M: Endothelin and endothelin receptor antagonists in systemic rheumatic disease. *Arthritis Rheum* 2003; 48: 1190-9.
4. ORAVEC R, BREDEMEIER M, LAURINO C, PINOTTI A, ROHDE L, BRENO J: NT-proBNP levels in systemic sclerosis: Association with clinical and laboratory abnormalities. *Clin Biochem* 2010; 43: 745-9.
5. NAGAYA N, NISHIKIMI T, UEMATSU M *et al*.: Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000; 102: 865-70.
6. 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.
7. VESTBO J, AGUSTI A, ANZUETO A *et al*.: Global Initiative For Chronic Obstructive Pulmonary Disease; Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (updated 2010) [homepage on the Internet]. Available from: http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf
8. Medal.org [homepage on the Internet]. Institute for Algorithmic Medicine A Texas Non-profit Corporation. Available from: http://www.medal.org/irh/medal/ch22%5Cch22.22%5Cch22.22.04.php
9. KENDRICK KR, BAXI SC, SMITH RM: Usefulness of the modified 0-10 Borg scale in assessing the degree of dyspnea in patients with COPD and asthma. *J Emerg Nurs* 2000; 26: 216-22.
10. AMERICAN THORACIC SOCIETY. ATS STATEMENT: Guidelines for the Six-minute Walk Test This Official Statement of the American Thoracic Society was approved by the ATS Board of Directors March 2002. *Am J Respir Crit Care Med* 2002; 166: 111-7.
11. DEGANO B, SITBON O, SAVALE L *et al*.: Characterization of pulmonary arterial hypertension patients walking more than 450 m in 6 min at diagnosis. *Chest* 2010; 137: 1297-303.
12. TEI C, DUJARDIN KS, HODGE DO *et al*.: Doppler echocardiographic index for assessment of global right ventricular function. *J Am Soc Echocardiogr* 1996; 9: 838-47.
13. MIYAMOTO S, NAGAYA N, SATOH T *et al*.: Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. *Am J Respir Crit Care Med* 2000; 161: 487-92.
14. IMPENS AJ, WANGKAEW S, SEIBOLD JR: The 6-minute walk test in scleroderma – how measuring everything measures nothing. *Rheumatology* 2008; 47: 68-9.
15. RUBIN LJ, BADESCH DB, BARST RJ *et al*.: Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896-903.
16. MORIELLO C, FINCH L, MAYO NE: Relationship between muscle strength and functional walking capacity among people with stroke. *J Rehabil Res Dev* 2011; 48: 267-75.
17. GARIN MC, HIGHLAND KB, SILVER RM, STRANGE C: Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma. *J Rheumatol* 2009; 36: 330-6.
18. PAMIDI S, MEHTA S: Six-minute walk test in scleroderma-associated pulmonary arterial hypertension: are we counting what counts? Editorial. *J Rheumatol* 2009; 36: 216-8.
19. CIURZYŃSKI M, BIENIAS P, LICHODZIEJEWSKA B *et al*.: Non-invasive diagnostic and functional evaluation of cardiac involvement in patients with systemic sclerosis. *Clin Rheumatol* 2008; 27: 991-7.
20. HUEZ S, ROUFOSSE F, VACHIÉRY JL *et al*.:Isolated right ventricular dysfunction in systemic sclerosis: latent pulmonary hypertension? *Eur Respir J* 2007; 30: 928-36.
21. VILLALBA WO, SAMPAIO-BARROS PD, PEREIRA MC: Six-minute walk test for the evaluation of pulmonary disease severity in scleroderma patients. *Chest* 2007; 131: 217-22.
22. YAMANE K, MIYAUCHI T, SUZUKI N *et al*.: Significance of plasma endothelin-1 levels in patients with systemic sclerosis. *J Rheumatol* 1992; 19: 1566-71.
23. YAMANE K, KASHIWAGI H, SUZUKI N *et al*.: Elevated plasma levels of endothelin-1 in systemic sclerosis. *Arthritis Rheum* 1991; 34: 243-4.
24. CORAL-ALVARADO P, QUINTANA G, GARCES MF *et al*.: Potential biomarkers for detecting pulmonary arterial hypertension in patients with systemic sclerosis. *Rheumatol Int* 2009; 29: 1017-24.
25. WILLIAMS MH, HANDLER CE, AKRAM R *et al*.: Role of N-terminal brain natriuretic peptide (NT-proBNP) in scleroderma-associated pulmonary arterial hypertension. *Eur Heart J* 2006; 27: 1485-94.
26. RUDSKI L, LAI W, AFILALO J *et al*.: Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A report from the American Society of Echocariography. *J Am Soc Echocardiogr* 2010; 23: 685-713.
27. DEUSCHLE K, WEINERT K, BECKER MO, BACKHAUS M, HUSCHER D, RIEMEKASTEN G: Six minute walk distance as a marker for disability and complaints in patients with systemic sclerosis. *Clin Exp Rheumatol* 2011; 29 (Suppl. 65): S53-9.
28. SCHMIDT J, LAUNAY D, SOUDAN B *et al*.: Assessment of plasma endothelin level measurement in systemic sclerosis. *Rev Med Interne* 2007; 28: 371-6.
29. CHIGHIZOLA C *et al*.: Role of N-terminal pro-brain natriuretic peptide in detecting clinically significant cardiac involvement in systemic sclerosis patients. *Clin Exp Rheumatol* 2012; 30 (Suppl. 71): S81-5.
30. DE GROOTE P, GRESSIN V, HACHULLA E *et al*.: Evaluation of cardiac abnormalities by Doppler echocardiography in a large nationwide multicentric cohort of patients with systemic sclerosis. *Ann Rheum Dis* 2008; 67: 31-6.
31. CIURZYNSKI M, BIENIAS P, LICHODZIEJEWSKA B *et al*.: Assessment of left and right ventricular diastolic function in patients with systemic sclerosis. *Kardiol Pol* 2008; 66: 269-76.
32. HINCHCLIFF M, DESAI CS, VARGA J, SHAH SJ: Prevalence, prognosis, and factors associated with left ventricular diastolic dysfunction in systemic sclerosis. *Clin Exp Rheumatol* 2012; 30 (Suppl. 71): S30-7).