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Contribution of Speckle Tracking to Estimation of Pulmonary Hypertension by Standard Doppler Echocardiography in Patients with Systemic Sclerosis and MCTD

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Abstract

Objectives: Development of pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) represents one of the most serious complications. The study aimed at assessing right ventricular (RV) global longitudinal strain and its relation to pulmonary artery pressure.

Methods: Echocardiography was performed in 74 patients of whom 60 had SSc and 14 had mixed connective tissue disease (MCTD). Besides routine left and right ventricle assessment and pulmonary pressure estimation by Doppler echocardiography, RV fractional area change (FAC) and 2D strain of the RV free wall were evaluated. At the same time, levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin T and auto-antibodies were measured and all patients had diffusing capacity of the lung for carbon monoxide (DLCO) determined. All patients with probable PAH underwent right heart catheterization.

Results: Pulmonary hypertension was found to be unlikely in 59 patients (79.7%), possible in 10 patients (13.5%) and probable in 5 patients (6.7%). Significant associations were found between pulmonary artery systolic pressure (PASP) and RV free wall global longitudinal strain (r=0.292; p=0.023), between PASP and NT-proBNP (r=0.436; p=0.001) and between PASP and FAC (r=0.320; p=0.005). Pulmonary artery systolic pressure did not correlate with left ventricular systolic or diastolic function parameters in this cohort.

Conclusion: Speckle tracking of the RV represents a useful additional tool in RV assessment in relation to PH in SSc and MCTD patients; right heart catheterization remains an essential method for PAH confirmation.

Keywords: Systemic sclerosis; Pulmonary hypertension; Speckle tracking

Introduction

Pulmonary arterial hypertension (PAH) is a serious and life-limiting organ complication of systemic sclerosis (SSc). The non-invasive diagnosis relies mainly on estimation of pulmonary artery systolic pressure (PASP) by transthoracic echocardiography [1]. Impaired diffusing capacity of the lung for carbon monoxide (DLCO) and elevated serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are considered as SSc-PAH predictors [2]. Novel parameters obtained by echocardiography such as deformation analysis derived from 2D speckle tracking have been used recently in SSc patients for both left [3] and right [4] ventricle assessment but not for SSc-associated PAH. The aim of this study was to evaluate the contribution of measuring right ventricular global longitudinal strain (RV-GLS) and other parameters of right ventricular (RV) systolic and diastolic function to the diagnosis of PAH in patients with SSc and related diseases.

Materials and Methods

A group of 74 patients, comprising 60 patients with SSc (51 females, mean age 58.86 ± 11.88 years; 9 males, mean age 57.55 ± 11.57 years) further divided into diffuse and limited SSc and 14 patients with mixed connective tissue disease (MCTD; 13 females, mean age 46.619 ± 10.98 years; 1 male aged 36 year) were examined by echocardiography. The examination was performed with the Philips iU 22 ultrasound system (S5-1 sector array transducer, 5 to 1 MHz operating frequency range) by a single experienced cardiologist (more than 7500 examinations, specializing in echocardiography in connective tissue diseases) to minimize interindividual variability. Pulmonary artery systolic pressure was determined from the sum of tricuspid regurgitation peak pressure gradients and right atrial pressure estimated from the inferior vena cava diameter and collapsibility in accordance with the current recommendations [1].

Additionally, RV fractional area change (FAC) and right atrial area were measured. Two-dimensional strain of the RV free wall derived from speckle tracking was evaluated with the PHILIPS QLAB 9.1 software. Spirometry and DLCO measurements were performed on the Jaeger MasterScreen body plethysmograph. Troponin T and NT-

proBNP serum levels were measured by electro-chemiluminescence immunoassay (Hitachi Cobas 8000 analyzer) using the Roche Diagnostics standardized kits Troponin T hs (cut-off value 0.014 ng/mL) and proBNP II (cut-off value 125 ng/L). Antibodies were tested by enzyme-linked immunosorbent assay (Tecan Sunrise microplate reader; Tecan HydroFlex microplate washer),ENA (MASTAZYME ENA Screen 7, cat. No. 733023), anti-Scl-70 and anti-centromere autoantibodies (MASTAZYME ANA Profil HJS), quantitative detection of anti-nucleosome antibodies (5B28L Anti-Nucleosome; negative cut-off value ≤ 20 U/mL, positive cut-off value >20 U/ml). In compliance with the arbitrary criteria for estimating the likelihood of PAH [1], patients were divided into three categories: Category 1–PAH unlikely (tricuspid regurgitation [TR] Vmax <2.8 m/s; PASP <36 mmHg; normal RV function without RV hypertrophy), Category 2–PAH possible (TR Vmax 2.8–3.4 m/s; PASP 36–50 mmHg or PASP <36 mmHg and suspected RV hypertrophy and/or dilatation and RV dysfunction) and Category 3–PAH probable (TR Vmax >3.4 m/s; PASP >50 mmHg; evidence or absence of RV hypertrophy/dilatation and RV dysfunction). All patients with probable PAH and symptomatic patients with possible PAH on echocardiography underwent right heart catheterization (RHC).

For statistical analysis, the SPSS Statistics v.15 was used; all tests were performed at a significance level of 0.05. As the Shapiro-Wilk test showed that most of the variables were not normally distributed, nonparametric methods were used. Correlations of quantitative variables were verified by calculating Spearman's coefficients. The relationship between autoantibody positivity and echocardiography and spirometry parameters was verified with the Mann-Whitney U test. Dependency on diagnosis was tested by the Kruskal-Wallis test; in case of statistically significant results, multiple comparisons in pairs were performed with the Mann-Whitney U test. The significance level was adjusted using the Bonferroni correction.

Results

Echocardiographic Parameters: Pulmonary arterial hypertension was found as unlikely in 59 (79.7%) patients, possible in 10 (13.5%) patients and probable in 5 (6.7%) patients (Table 1). A significant correlation was found between PASP and global longitudinal strain of the RV free wall (p=0.023), most notably between PASP and strain the RV free wall medial segment (RV-S med; Figure 1).

RV-FAC correlated negatively with both PASP (r=0.320, p=0.05; Figure 2) and right atrial area (r=0.509, p=0.002). Validity of PASP estimation was confirmed by a strong correlation between PASP determined by echocardiography and PASP measured in catheterized patients (PASPcath, r=0.873). PASPcath was also strongly correlated with RV-GLS (r=0.793, p=0.033), FAC (r=0.857, p=0.014) and tricuspid annular plane systolic excursion (TAPSE) (r=0.929, p=0.003). In the cohort, PASP did not correlate with left ventricular systolic or diastolic function.

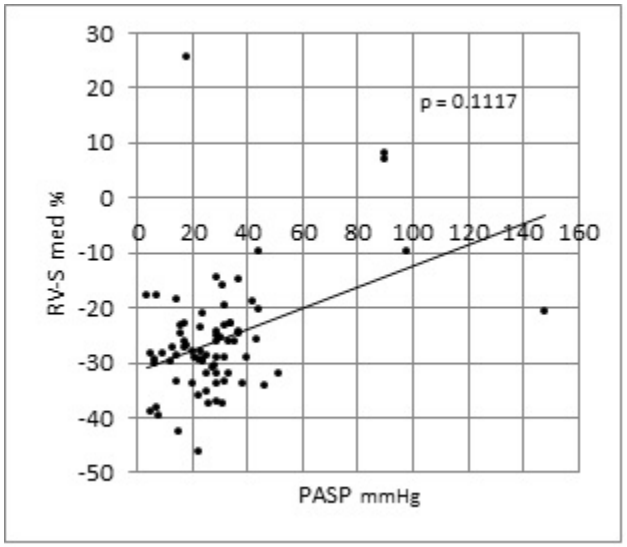

Figure 1: Spearman's correlation of PASP and RV-S med; PASP-pulmonary artery systolic pressure, RV-S med-right ventricular strain-medial segment.

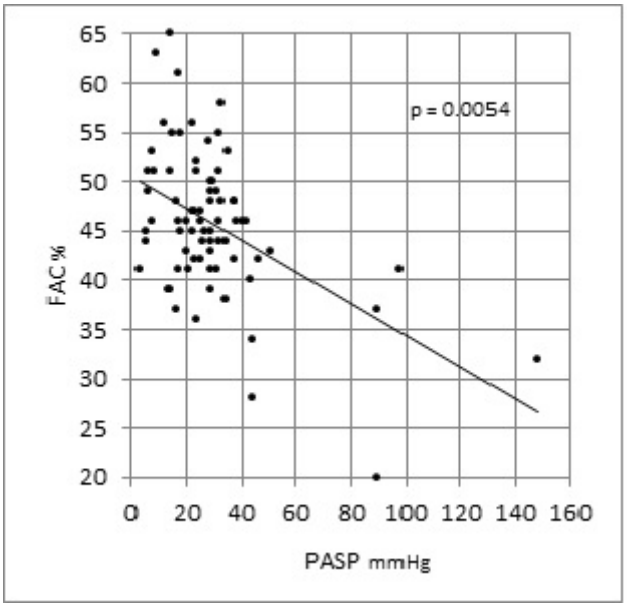

Figure 2: Spearman's correlation of PASP and FAC; PASP-pulmonary artery systolic pressure, FAC - fractional area change.

	PASP <36 mmHg	PASP 36-50 mmHg	PASP >50 mmHg	P*
n (%)	59 (79.7%)	10 (13.5%)	5 (6.7%)	
LVEF%	62 ± 6.5	63.4 ± 7.7	65.8 ± 7.36	0.769
RVD PLAX mm	28.97 ± 4.24	29.3 ± 3.94	34.8 ± 7.82	0.116
RVD A4C mm	39.16 ± 5.16	29.3 ± 3.94	34.8 ± 7.82	0.426
FAC%	47.47 ± 6.32	42.0 ± 6.53	34.6 ± 9.18	0.002
RAA cm^2	15.15 ± 3.88	18.32 ± 5.39	19.7 ± 0.85	0.024
TAPSE mm	25.4 ± 3.0	23.7 ± 4.8	17.3 ± 6.3	0.024
TASV cm/s	12.94 ± 2.15	14.28 ± 4.14	10.42 ± 2.67	0.023
RV-GLS%	-25.59 ± 5.41	-22.90 ± 7.61	-14.4 ± 9.00	0.023
RV-S bas%	-28.67 ± 6.47	-29.67 ± 9.29	-18.08 ± 7.85	0.030
RV-S med%	-27.79 ± 9.58	-23.60 ± 7.86	-9.42 ± 17.33	0.017
RV-S api%	-27.17 ± 8.28	-24.55 ± 11.97	-17.77 ± 10.66	0.084
troponin T ng/mL	0.016 ± 0.016	0.051 ± 0.052	3.76 ± 7.49	0.18
NT-proBNP ng/L	172 ± 261	1009 ± 1913	1778 ± 1009	0.00001
DLCO%	63.9 ± 15.2	46.2 ± 18.4	40.0 ± 14.3	0.002

PASP: Pulmonary Artery Systolic Pressure; LVEF: Left Ventricular Ejection Fraction; RVD PLAX: Right Ventricular Diameter In The Parasternal Long Axis View; RVD A4C: Right Ventricular Diameter In The Apical Four-Chamber View; FAC: Fractional Area Change; RAA: Right Atrial Area; TAPSE: Tricuspid Annular Plane Systolic Excursion; TASV : Tricuspid Annular Systolic Velocity Measured By Tissue Doppler Imaging; RV-GLS : Right Ventricular Global Longitudinal Strain: RV-S bas: Right Ventricular Strain Basal Segment; RV-S med: Right Ventricular Strain Medial Segment; RV-S api: Right Ventricular Strain Apical Segment; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide; DLCO: Diffusing Capacity Of The Lung For Carbon Monoxide; *Kruskal-Wallis test.

Table 1: Selected characteristics in cohort subpopulations by category of pulmonary hypertension (n=74).

Serum Parameters: Serum levels of NT-proBNP correlated with PASP (r=0.436, p=0.001; Figure 3; due to a wide range of NT-proBNP values, the logarithm of NT-proBNP was used), PAH category (p=0.0002) and, negatively, with RV-FAC (r-0, 348, p=0.008). Troponin T did not show any significant correlation.

Diffuse Lung Capacity: Strongly statistically significant correlations were found between PAH category and DLCO (p=0.0028) and between DLCO and FAC (r=0.319, p=0.0006; Figure 4). Significantly lower DLCO was noted in patients with diffuse SSc (Table 2).

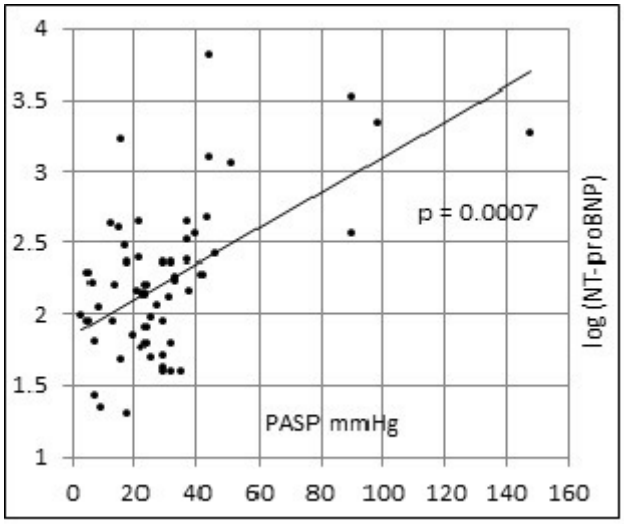

Figure 3: Spearman's correlation of NT-proBNP (displayed as log NT-proBNP) and PASP estimated by echocardiography; PASP: Pulmonary Artery Systolic Pressure; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide.

	SSc diffuse	SSc limited	MCTD	P*
n	30	30	14	
age	60.3 ± 11.0	56.6 ± 11.8	45.8 ± 10.9	0.001
LVEF%	63.1 ± 6.9	64.1 ± 6.3	62.2 ± 6.9	0.745
PASP mmHg	35.5 ± 30.5	23.5 ± 24.5	28.3 ± 25.0	0.315
FAC%	43.3 ± 8.17	47.9 ± 6.3	47.2 ± 6.53	0.096
TAPSE mm	23.4 ± 4.7	25.7 ± 2.8	25.9 ± 4.7	0.270
TASV cm/s	12.76 ± 3.25	13.04 ± 2.14	13.22 ± 2.04	0.742
RV GLS%	-22.5 ± 7.10	-26.7 ± 5.3	-24.14 ± 7.56	0.046
TLC%	90.3 ± 19.0	109.6 ± 25.9	103.6 ± 13.1	0.009
DLCO%	48.9 ± 16.9	67.5 ± 14.3	66.7 ± 13.2	0.0002

SSc: Systemic Sclerosis; MCTD: Mixed Connective Tissue Disease; LVEF: Left Ventricular Ejection Fraction; PASP: Pulmonary Artery Systolic Pressure; FAC: Fractional Area Change; TAPSE: Tricuspid Annular Plane Systolic Excursion; TASV: tricuspid annular systolic velocity measured by tissue doppler imaging; RV-GLS: Right Ventricular Global Longitudinal Strain; TLC: Total Lung Capacity; DLCO: Diffusing Capacity Of The Lung For Carbon Monoxide; *Kruskal-Wallis test.

Table 2: Selected characteristics in cohort subpopulations by type of connective tissue disease diagnosis (n=74).

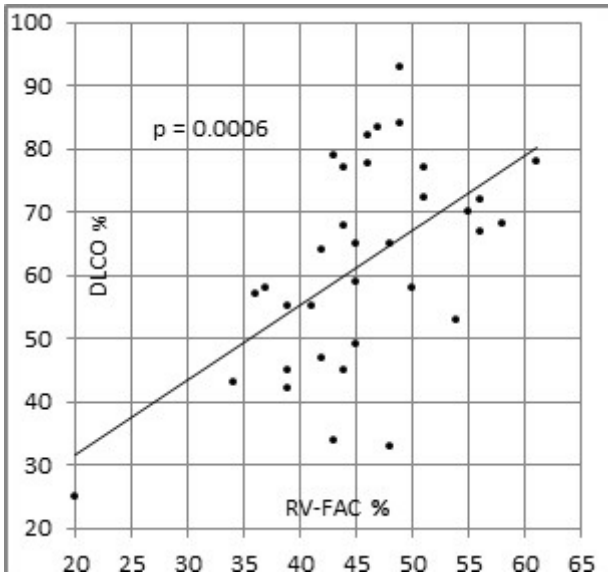

Figure 4: Spearman's correlation of RV-FAC and DLCO; RV-FAC: Right Ventricular Fractional Area Change; DLCO: Diffusing Capacity of The Lung For Carbon Monoxide.

Autoantibodies

Autoantibody analysis did not show any significant relation to PASP or other echocardiographic parameters. However, the Mann-Whitney U test showed differences in spirometry and DLCO measurements, with patients with positive anti-centromere antibodies having significantly lower total lung capacity (p=0.013) and anti-Scl-70-positive patients having lower DLCO.

Prediction of possible and probable PAH (Categories 2 and 3 by echocardiography): Cut-off values were calculated as follows: NT-proBNP 229.2 ng/L (sensitivity 86.7%, specificity 85.7%), FAC 44% (sensitivity 66.7%, specificity 74.6%), RV-S med 26.08% (sensitivity 73.3%, specificity 69.5%) and DLCO 59% (sensitivity 75.0%, specificity 65.4%).

Discussion

Systemic sclerosis is associated with serious and life-threatening manifestations, among which pulmonary hypertension belongs to the leading causes of mortality [2-5]. Patients with SSc-associated PAH have as much as three-fold worse prognosis than those with idiopathic PAH [6]. Age over 60 years, male sex and DLCO <39% are other significant predictors of mortality in patients with SSc-associated PAH [7]. The prevalence of PAH was 7.08% in a study of 203 SSc patients [8]. A larger Italian cohort (867 SSc patients) showed a lower rate of PAH prevalence (3.7%) [9]. Also in the present study, most of patients with SSc and MCTD screened by resting echocardiography had results showing low suspicion rates (PASP <36 mmHg). Probable PAH (PASP >50 mmHg) found by echocardiography in 5 (6.7%) patients was confirmed by RHC in all of them. But in symptomatic patients with possible PAH (PASP 36–50 mmHg) who were indicated for and also underwent RHC, PAH was excluded. Therefore, numerous authors have searched for both non-invasive and invasive predictors of pulmonary hypertension such as stress Doppler echocardiography [10] or invasively assessed exercise-induced pulmonary hypertension [11]. The latter could reveal more types of pulmonary hypertension including pulmonary venous hypertension and out-of-proportion PAH [12] and distinguish between exercise-induced PAH and diastolic dysfunction [13] but d invasive character and remaining problems, it DETECT study algorithm [14] provided clinicians with a helpful and evidence-based tool for identification of patients with a higher risk for PAH and indicated for RHC. However, there are some limitations to the use of the DETECT algorithm. The tool was designed primarily for high-risk patients (DLCO <60% and disease duration >3 years) included in the primary study and not all input parameters might be available in clinical practice. Speckle tracking and strain measurement performed in an experienced echocardiography laboratory have potential for adding useful information in the assessment of patients at risk for pulmonary hypertension but once again, this method is not a part of routine echocardiography. The benefit of speckle tracking and RV-GLS measurement in the diagnosis of pulmonary hypertension has been recently shown in several studies. Freed et al.demonstrated a correlation of 2D echocardiography-derived RV strain with cardiovascular magnetic resonance (CMR)-derived RV ejection fraction in 30 PAH patients [15]. Ikeda et al.showed RV peak systolic strain as the only independent factor associated with the mean pulmonary artery pressure ≥ 35 mmHg measured by RHC; the RV peak systolic strain cut-off value was 20.75%, similar to that found in the present study [16]. Conventional easy-to-measure RV function parameters such as TAPSE and tricuspid annular systolic velocity (TASV) confirmed a good correlation with PASP in both the echocardiography and catheterized patient groups of the present study. This is also consistent with results of a recent study by Focardi et al.comparing both conventional (TAPSE,TASV, FAC) and novel (RV strain) parameters with CMR, albeit in non-SSc patients [17].

From all laboratory markers, NT-proBNP seems to be the most powerful parameter for predicting pulmonary hypertension; the cut-off value of 229.2 ng/L calculated in our cohort showed the best ratio between specificity and sensitivity. Studies assessing NT-proBNP for the screening and diagnosis of PAH in connective tissue disease reported a similar cut-off >236 pg/mL and specificity of 83–100% for RHC-PAH [18]. Troponin T and most of the tested autoantibodies failed to show a relation to PAH in this study; anti-Scl-70 antibodies correlated with lower DLCO and anti-centromere autoantibodies correlated with lower total lung capacity. Grader-Beck et al.described an association of anti-4S-LacNAc antibodies with a higher prevalence of pulmonary hypertension in systemic scleroderma [19]. This observation deserves further investigation.

Thus, NT-proBNP and DLCO now belong to the most useful predictors of pulmonary hypertension in SSc patients [20,21]. Regarding differences between limited or diffuse SSc and MCTD in the present study, patients with MCTD were significant younger than SSc patients and patients with diffuse SSc had significant lower total lung capacity and DLCO than those with limited SSc or MCTD. This is consistent with a documented higher incidence of pulmonary involvement in diffuse SSc [22]. With the exception of RV-GLS which was lower in diffuse SSc (p=0.046), no other significant differences in echocardiographic parameters were observed between diffuse and limited SSc and MCTD patients. Thus, all differences in echocardiographic parameters were dependent on the presence of PAH and not on the disease subtype.

An active search for pulmonary hypertension is an important aspect of care for SSc patients. We realize that echocardiography is method

just to estimate pulmonary hypertension, as well as their novel modalities and other contributing factors and the right heart catheterization is necessary for diagnosis of pulmonary hypertension. Right heart catheterization remains the golden standard in the diagnosis of pulmonary hypertension and is indispensable before the decision is made on PAH-specific treatment influencing the life prognosis in these patients. Echocardiography is the first step in this screening activity and in addition to its established parameters in PASP estimation, supported by clinical signs and NT-proBNP levels, speckle tracking of the RV free wall seems to be a useful supplement. The limitations of this method are the condition of acceptable visibility of the RV free wall and necessity of post-processing which is time-consuming. Further research in this field and advances in echocardiography processing software will give an answer to the role of this method.

Ethics Approval

The study was conducted during routine patient follow-up and in accordance with the local applicable laws. Patients undergoing right heart catheterization gave informed consent.

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References

1. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, et al. (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 23: 685-713.
2. Khanna D, Gladue H, Channick R, Chung L, Distler O, et al. (2013) Recommendations for screening and detection of connective tissue disease-associated pulmonary arterial hypertension. Arthritis Rheum 65: 3194-3201.
3. Spethmann S, Rieper K, Riemekasten G, Borges AC, Schattke S, et al. (2014) Echocardiographic follow-up of patients with systemic sclerosis by 2D speckle tracking echocardiography of the left ventricle. Cardiovasc Ultrasound 12: 13.
4. Durmus E, Sunbul M, Tigen K, Kivrak T, Ozen G, et al. (2015) Right ventricular and atrial functions in systemic sclerosis patients without pulmonary hypertension: Speckle-tracking echocardiographic study. Herz 40: 709-715.
5. Hachulla E, Clerson P, Airò P, Cuomo G, Allanore Y, et al. (2015) Value of systolic pulmonary arterial pressure as a prognostic factor of death in the systemic sclerosis EUSTAR population. Rheumatology 54: 1262-1269.
6. Chung L, Farber HW, Benza R, Miller DP, Parsons L, et al. (201) Unique Predictors of Mortality in Patients With Pulmonary Arterial Hypertension Associated With Systemic Sclerosis in the Reveal Registry. Chest 146: 1494-1504.
7. Chung L, Domsic RT, Lingala B, Alkassab F, Bolster M, et al. (2014) Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry. Arthritis Care Res 66: 489-495.
8. Jansa P, Becvar R, Ambroz D, Palecek T, Tomcik M, et al. (2012) Pulmonary arterial hypertension associated with systemic sclerosis in the Czech Republic. Clin Rheumatol 31: 557-561.
9. Ludici M, Codullo V, Giuggioli D, Riccieri V, Cuomo G, et al. (2013) Pulmonary hypertension in systemic sclerosis: prevalence, incidence and predictive factors in a large multicentric Italian cohort. Clin Exp Rheumatol 31 Suppl 76: 31-36.
10. Codullo V, Caporali R, Cuomo G, Ghio S, D'Alto M, et al. (2013) Stress Doppler echocardiography in systemic sclerosis: evidence for a role in the prediction of pulmonary hypertension. Arthritis Rheum 65: 2403-2411.
11. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM (2008) Exercise-induced pulmonary arterial hypertension. Circulation 118: 2183-2189.
12. Saggar R, Khanna D, Furst DE, Shapiro S, Maranian P, et al. (2010) Exercise-induced pulmonary hypertension associated with systemic sclerosis: four distinct entities. Arthritis Rheum 62: 3741-3750.
13. Hager WD, Collins I, Tate JP, Azrin M, Foley R, et al. (2013) Exercise during cardiac catheterization distinguishes between pulmonary and left ventricular causes of dyspnea in systemic sclerosis patients. Clin Respir J 7: 227-236.
14. Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, et al. (2014) Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 73:1340-1349.
15. Freed BH, Tsang W, Bhave NM, Patel AR, Weinert L, et al. (2015) Right Ventricular Strain in Pulmonary Arterial Hypertension: A 2D Echocardiography and Cardiac Magnetic Resonance Study. Echocardiography 32: 257–263.
16. Ikeda S, Tsuneto A, Kojima S, Koga S, Nakata T, et al. (2014) Longitudinal strain of right ventricular free wall by 2-dimensional speckle-tracking echocardiography is useful for detecting pulmonary hypertension. Life Sci 111: 12-17.
17. Focardi M, Cameli M, Carbone SF, Massoni A, De Vito R, et al. (2015) Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. Eur Heart J Cardiovasc Imaging 16: 47-52.
18. Gladue H, Altorok N, Townsend W, McLaughlin V, Khanna D (2014) Screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension: a systematic review. Semin Arthritis Rheum 43: 536-541.
19. Grader-Beck T, Boin F, von Gunten S, Smith D, Rosen A, et al. (2011) Antibodies recognising sulfated carbohydrates are prevalent in systemic sclerosis and associated with pulmonary vascular disease. Ann Rheum Dis 70: 2218-2224.
20. Allanore Y, Borderie D, Avouac J, Zerkak D, Meune C, et al. (2008) High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 58: 284-291.
21. Thakkar V, Stevens W, Prior D, Youssef P, Liew D, et al. (2013) The inclusion of N-terminal pro-brain natriuretic peptide in a sensitive screening strategy for systemic sclerosis-related pulmonary arterial hypertension: a cohort study. Arthritis Res Ther 15: R193.
22. Nihtyanova SI, Tang EC, Coghlan JG, Wells AU, Black CM, et al. (2010) Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study. QJM 103: 109-115.