



ELSEVIER

Contents lists available at ScienceDirect

## Advances in Medical Sciences

journal homepage: [www.elsevier.com/locate/advms](http://www.elsevier.com/locate/advms)

Original research article

## Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary circulation in patients with systemic sclerosis

Michał Ciurzyński<sup>a,\*</sup>, Piotr Bienias<sup>a</sup>, Katarzyna Ciesielska<sup>a</sup>, Anna Chrzanowska<sup>a</sup>,  
Iwona Dudzik-Niewiadomska<sup>a</sup>, Katarzyna Kurnicka<sup>a</sup>, Justyna Domienik-Karłowicz<sup>a</sup>,  
Maria Siwicka<sup>b</sup>, Piotr Sobieraj<sup>c</sup>, Agnieszka Kalińska-Bienias<sup>d</sup>, Marcin Kurzyzna<sup>e</sup>, Piotr Pruszczyk<sup>a</sup>

<sup>a</sup> Department of Internal Medicine and Cardiology, Medical University of Warsaw, Warsaw, Poland<sup>b</sup> Department of Dermatology, Medical University of Warsaw, Warsaw, Poland<sup>c</sup> Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Warsaw, Poland<sup>d</sup> Department of Dermatology and Immunodermatology, Medical University of Warsaw, Warsaw, Poland<sup>e</sup> Department of Pulmonary Circulation and Thromboembolic Diseases, Medical Center of Postgraduate Education, European Health Centre - Otwock, Otwock, Poland

## ARTICLE INFO

## Keywords:

Systemic sclerosis  
Pulmonary hypertension  
Doppler echocardiography  
Exercise

## ABSTRACT

**Purpose:** Pulmonary hypertension (PH) is an ominous complication in systemic sclerosis patients (SSc) and echocardiography is a screening tool for its detection. The goal of this study was to assess the reliability of resting and exercise echo Doppler parameters with data obtained by right heart catheterization (RHC).

**Material and methods:** We included 91 patients (84 F, 53.3 ± 15.2 years) with SSc. Transthoracic echocardiography followed by exercise Doppler-echocardiography (EDE) were performed. A positive EDE was defined as a ≥ 20 mmHg increase in tricuspid regurgitation peak gradient (TRPG). RHC with exercise was performed in positive EDE patients and/or in subjects with resting TRPG > 31 mmHg.

**Results:** Finally, RHC was performed in 20 patients. The correlation for the echocardiography and invasive measurement of systolic (sPAP) and mean (mPAP) pulmonary artery pressure was  $r = 0.66$  ( $p = 0.001$ ) and  $r = 0.7$  ( $p = 0.001$ ), respectively. We also found significant correlation between echocardiography and invasive measurement of exercise sPAP  $r = 0.68$  ( $p = 0.001$ ) and exercise mPAP  $r = 0.67$  ( $p = 0.002$ ). There was a correlation between pulmonary vascular resistance (PVR) assessed by echocardiography and measured by RHC  $r = 0.49$ ,  $p = 0.027$ . The equation derived within our population was:  $PVR \text{ by echocardiography} = 9.6 \cdot TRV / TVI_{RVOT} + 0.068$ . We also performed ROC analysis to predict  $PVR > 2 \text{ WU}$ . Our results highlight that sPAP has the highest AUC (0.802, 95% CI 0.585–1).

**Conclusion:** Doppler resting and exercise echocardiography may provide a reliable, noninvasive method for determining resting and exercise sPAP, mPAP, and PVR in SSc patients, although it may underestimate or overestimate these values in some individuals. Doppler echocardiography does not replace RHC for definite hemodynamic assessment of suspected PH.

## 1. Introduction

Pulmonary arterial hypertension (PAH) is a leading cause of mortality in patients with systemic sclerosis (SSc). PAH affects 8–15% of patients with SSc with a median survival of 1.5–2 years [1,2]. In SSc patients, PAH may occur in association with interstitial fibrosis or as a result of an isolated pulmonary arteriopathy. In addition, venous pulmonary hypertension (PH) due to left heart disease may be present. It is imperative to determine the mechanism of PH because of its influence on treatment selection. Right heart catheterization (RHC) is still the

definitive test in the diagnosis of PH [3]. However, it is an impractical screening tool because of its invasive character. Echo Doppler is a noninvasive, easily available method, with potential value in the identification of PH. It provides several indices which correlate with right heart hemodynamic parameters. However, it was underlined that Doppler-derived pressure estimation may be inaccurate in the individual cases [4]. According to the current European Society of Cardiology guidelines on PAH, echocardiographic screening for the detection of PH has been recommended annually in symptomatic patients and may be considered in asymptomatic patients with scleroderma [3].

\* Corresponding author at: Department of Internal Medicine and Cardiology, Medical University of Warsaw, Lindeya 4, 02-005, Warsaw, Poland.

E-mail address: [michal.ciurzynski@wum.edu.pl](mailto:michal.ciurzynski@wum.edu.pl) (M. Ciurzyński).

<https://doi.org/10.1016/j.advms.2019.03.006>

Received 21 October 2018; Accepted 26 March 2019

Available online 08 April 2019

1896-1126/ © 2019 Published by Elsevier B.V. on behalf of Medical University of Białystok.

Moreover, repeated echocardiography is useful in monitoring of hemodynamic status in pharmacologically treated patients. Hemodynamic parameters are most often measured at rest, however patients usually experience dyspnea on exertion. Therefore exercise echocardiography may potentially be useful for the detection of an “exaggerated pulmonary artery pressure response to exercise” (EPAPR) [4,5]. In a recent official statement of the European Respiratory Society on pulmonary hemodynamics during exercise, Kovacs et al. [6] underlined that exercise Doppler echocardiography (EDE) is a non-invasive tool with evolving clinical application. However the clinical value of EDE for PH diagnosis is still uncertain. The goal of this study was to assess the reliability of resting and EDE parameters with data obtained by RHC.

## 2. Materials and methods

Ninety one consecutive SSc patients (84 females and 7 males; mean age  $53.3 \pm 15.2$  years), with mean time of  $9 \pm 12.4$  years from SSc diagnosis, were prospectively included in the study.

All SSc patients fulfilled the 2013 European League Against Rheumatism/American College of Rheumatology classification criteria [7]. Fifty five (60%) patients were classified as having diffuse SSc (dSSc), while 36 (40%) had limited SSc (lSSc).

Patients with coronary artery disease (angina pectoris, previous myocardial infarction, electrocardiographic and/or echocardiographic signs of myocardial ischemia), essential arterial hypertension, left ventricle (LV) hypertrophy (intraventricular septum or posterior wall  $> 11$  mm at echocardiographic examination), significant valvular abnormalities or systolic left ventricular failure (ejection fraction  $< 50\%$ ) were not included in the current study. Grade III diastolic dysfunction with  $E/A \geq 2$  was also an exclusion criterion [8].

Moreover, SSc patients with significant pulmonary functional abnormalities (defined by forced vital capacity - FVC, total lung capacity - TLC, or forced expiratory volume in 1 s - FEV<sub>1</sub>  $< 60\%$  of predicted value) were also not included. We also did not include patients with significant fibrotic changes in the lung revealed by high-resolution computed tomography (Kazerooni fibrosis score  $\geq 16$ ). In addition, signs and symptoms suggestive of chronic thromboembolic pulmonary hypertension (CTEPH) were also treated as exclusion criteria.

An impaired renal function with creatinine clearance calculated by Modification of Diet in Renal Disease Study Group (MDRD) formula to be below 60 ml/min was also an exclusion criterion.

### 2.1. Clinical features and visceral involvement

Clinical evaluation of the signs and symptoms of SSc was performed in all patients. Pulmonary involvement was assessed by chest radiography, high resolution computed tomography, pulmonary function testing and measurement of single breath diffusing lung capacity for carbon monoxide (DLCO).

### 2.2. Transthoracic echocardiography

Echocardiographic examination was performed with Philips iE33 (Philips Medical Systems, Andover, MA, USA) with 2.5–3.5 MHz transducers. Patients were examined in the left lateral position. The dimensions of the right and left ventricles were measured in the parasternal long-axis view and apical four chamber view in the late diastole defined by the R wave of the monitored electrocardiogram. From the subcostal approach vena cava dimensions at spontaneous inspiration and expiration were measured.

After recording of the tricuspid valve peak systolic velocity (TRV) with continuous-wave Doppler echocardiography, the tricuspid regurgitation peak gradient (TRPG) was calculated according the simplified Bernoulli equation:  $TRPG = 4v^2$ , where “v” is the peak velocity of the tricuspid regurgitation jet (m/s). Right atrial pressure (RAP) was

estimated by evaluating the inferior vena cava (IVC) size and change with respiration [9]. RAP was estimated to be 5 mmHg when the IVC diameter was less than 20 mm with its respiratory collapsibility greater than 50%; 10 mmHg when IVC diameter was less than 20 mm and collapsibility less than 50%; 15 mmHg when IVC diameter was greater than 20 mm and the collapsibility greater than 50%; and 20 mmHg when IVC diameter was greater than 20 mm and the collapsibility was less than 50%. PH was suspected with any TRPG  $> 31$  mmHg (tricuspid regurgitant velocity  $> 2.8$  m/s) [3]. The pulmonary artery systolic pressure (sPAP) was calculated according the equation:  $sPAP = TRPG + RAP$  [3]. Mean pulmonary artery pressure (mPAP) was derived according to the formula:  $mPAP = 0.61 * sPAP + 2$  mmHg [10]. The right ventricular outflow tract time-velocity integral (TVI<sub>RVOT</sub>; cm) was obtained using pulse wave Doppler with sample volume placed in the right ventricular (RV) outflow tract just below the pulmonary valve. The PVR in Wood units (WU) was calculated using the equation:  $10 * TRV / TVI_{RVOT} + 0.16$  [11]. The LV ejection fraction (EF) was calculated according to the modified Simpson rule using apical four- and two-chamber views.

### 2.3. The exercise echocardiography protocol

According to the Bruce protocol, all patient performed a standard exercise on a treadmill until 85% of maximum heart rate was achieved. The exercise was then stopped and the patient resumed the left lateral position as soon as possible. In the apical 4-chamber view, using continuous-wave Doppler, the peak velocity of the tricuspid regurgitant wave was recorded and the TRPG was calculated. The TRPG was recorded within one minute of stopping exercise. PH was suspected when TRPG at rest exceeded 31 mmHg ( $V_{max} > 2.8$  m/s) or increased by at least 20 mmHg vs baseline following exercise [5,12]. Patients with suspicion of PH were referred for RHC.

### 2.4. Hemodynamic assessment of the right heart

Cardiac catheterization was performed within 6 weeks of EDE according to the previously described protocol [13]. The Swan-Ganz catheter was passed under fluoroscopic guidance to the pulmonary artery. The following variables were recorded: PAP (systolic, diastolic and mean), mean pulmonary capillary wedge pressure (PCWP) and mean RAP.

Cardiac output was determined by thermodilution injecting cooled saline until a variability of less than 10% was achieved in 3 consecutive measurements. The vascular resistance values in pulmonary and systemic circulation were calculated using typical formulas. The exercise test was performed on a cycle ergometer in the supine position, aiming to achieve the maximum load of 125 W. After 5 min of maximal tolerated exercise the same measurements as those at rest were performed.

In accordance with the European Society of Cardiology (ESC) recommendations, PAH at rest was diagnosed when mPAP was  $\geq 25$  mmHg and PCWP did not exceed 15 mmHg [3]. Exaggerated pulmonary artery pressure response to exercise (EPAPR) with normal PCWP was identified when mPAP during exercise exceeded 30 mmHg in the presence of normal PCWP. The venous PH at rest was diagnosed when mPAP at rest was  $\geq 25$  mmHg and PCWP exceeded 15 mmHg [3]. EPAPR with elevated PCWP was diagnosed when mPAP during exercise exceeded 30 mmHg and PCWP exceeded 20 mmHg [5,12].

### 2.5. Statistical analysis

This is a prospective observational cohort study. Continuous data are presented as means and standard deviations and/or as medians followed by minimum-maximum ranges. Discrete variables were presented as numbers with percentages. Normality of distribution of continuous variables was verified using the Shapiro-Wilk test. Pearson or Spearman correlation coefficients were used depending on distribution

of analyzed parameters. Linear regression was used to establish the relation between PVR by echocardiography and TRV/TVI<sub>RVOT</sub> ratio. Bland-Altman statistics were used to assess agreement between echocardiographic and invasive measurements. Bias and estimated lower (LLoA) and upper limits of agreement (ULoA) with 95% confidence intervals were reported. LLoA and ULoA were estimated, as described by Bland and Altman, as the mean  $\pm$  2 standard deviations, with 95% confidence intervals. Interpretation of limits of agreement assumed a normal distribution of the differences between echocardiographically and invasively obtained pressures. ROC curves were used to present area under curve (AUC) of echocardiographic measurements for identifying patients with PVR > 2 WU. Results of the tests used were considered statistically significant at  $p < 0.05$ . All computations were performed in R, environment for statistical computations (ver. 3.4.0, Vienna, Austria).

## 2.6. Ethical issues

Ethical approval (number KB/269/2012) for this study was provided by the Ethical Committee of the Medical University of Warsaw, Warsaw, Poland. All patients gave their informed consent. The study was conducted in accordance with the 1964 Helsinki declaration with its later amendments.

## 3. Results

Ninety one patients were enrolled in the study. Four patients were excluded because they could not exercise adequately. Table 1 illustrates the demographic features and main clinical, findings of the remaining 87 SSc patients.

### 3.1. Echocardiographic and exercise data

Echocardiographic and exercise parameters of 87 SSc patients are presented in Table 2. Twenty two patients had resting TRPG > 31 mmHg. In 13 of them, both resting TRPG > 31 mmHg and TRPG increases > 20 mmHg during exercise were recorded. In 8 patients with TRPG < 31 mmHg at rest an increase of TRPG > 20 mmHg during exercise was also noticed.

Thirty SSc patients were referred for RHC. However, 8 refused, 1 deteriorated and could not participate and 1 died while awaiting the procedure. Finally, RHC was done in 20 SSc patients.

**Table 1**

Clinical data of SSc patients (n = 87).

Characteristics	Mean	Median, range
Age (years)	53.3 $\pm$ 15.2	
F/M gender (n)	81/6	
Disease duration (years)	9 $\pm$ 12.4	5.0 (1-25)
Rodnan Score	6.4 $\pm$ 6.7	4.0 (1-35)
Cutaneous involvement	No.	%
Diffuse	51	58
Limited	36	42
Autoantibodies		
ANA positive	82	94
ACA positive	26	30
Anti Scl 70 positive	44	51
DLCO, % predicted (n = 59)	70.7 $\pm$ 19	
6MWT distance (m)	510.4 $\pm$ 101.4	
NT-proBNP (pg/ml)		132.6 (21.5-17670)

ACA – anti-centromere antibodies; ANA – antinuclear antibodies; DLCO – carbon monoxide diffusing capacity; NT-proBNP – N-terminal pro-brain natriuretic peptide; 6MWT – 6-minute walk test.

**Table 2**

Echocardiographic and exercise parameters in SSc patients.

Variables	SSc patients (n = 87)
<b>Echocardiographic</b>	
EF (%)	66 $\pm$ 3.9
Resting TRPG (mmHg)	31.8 $\pm$ 4.9
LA diameter (mm)	33.5 $\pm$ 5.1
IVC expiration (mm)	16.0 $\pm$ 2.9
IVC inspiration (mm)	12.2 $\pm$ 2.7
<b>Exercise</b>	
Time exercise (min)	6.1 $\pm$ 2.5
Resting heart rate (bpm)	81.7 $\pm$ 18.7
Maximal heart rate (bpm)	149.6 $\pm$ 22.8
METS achieved	8.3 $\pm$ 2.4
Exercise TRPG (mmHg)	40.3 $\pm$ 14.1
$\Delta$ TRPG (mmHg)	12.9 $\pm$ 8.5

EF - ejection fraction; TRPG - tricuspid regurgitation peak gradient; LA - left atrium; IVC - diameter of inferior vena cava; METS - metabolic equivalents.

### 3.2. Echocardiographic and right heart catheterization parameters in 20 SSc patients with positive resting and/or exercise echocardiogram

The mean PCWP was 11.2  $\pm$  3.4 mmHg at rest, and 22.6  $\pm$  6.1 mmHg during exercise. In 12 (60%) of the patients an EPAP with elevated PCWP was observed (mean exercise mPAP 41.8  $\pm$  13.2 mmHg, mean exercise PCWP 25.1  $\pm$  4.8 mmHg). In remaining patients, 2 were diagnosed with PAH, 1 with venous PH, and 5 with an EPAP with normal PCWP.

### 3.3. Comparison of echocardiographic and right heart catheterization parameters in 20 SSc patients with positive resting and/or exercise echocardiogram

Correlation coefficients with confidence intervals and Bland-Altman statistics for echocardiographic and invasive hemodynamic measurements are presented in Table 3.

The correlation coefficient for the echocardiography and invasive measurement of sPAP was  $r = 0.66$ ,  $p = 0.001$  (Fig. 1, panel A). There was a significant correlation between mPAP calculated by echocardiography and RHC  $r = 0.7$ ,  $p = 0.001$  (Fig. 1, panel B). We also found a significant correlation between echocardiography and invasive measurement of exercise sPAP  $r = 0.68$ ,  $p = 0.001$  (Fig. 1, panel C) and exercise mPAP  $r = 0.67$ ,  $p = 0.002$  (Fig. 1, panel D). There was also a significant correlation between PVR assessed by echocardiography and measured by RHC  $r = 0.49$ ,  $p = 0.027$  (Fig. 1, panel E).

Using linear regression, we derived the equation describing the relationship between PVR by echocardiography and TRV/TVI<sub>RVOT</sub> ratio to be: PVR by echocardiography = 9.6\*TRV/TVI<sub>RVOT</sub> + 0.068 ( $p$ -value < 0.001).

The ROC curves and the areas under the curves (AUC) for the TRPG, the pulmonary artery (PA) systolic pressure, and the TRV/TVI<sub>RVOT</sub> ratio to predict PVR > 2 are shown in Fig. 2.

## 4. Discussion

Recently published guidelines of ESC on PH underlined that for final PH diagnosis RHC is still necessary [3]. mPAP above 25 mmHg calculated during RHC allows for PH diagnosis. However, RHC is an invasive method, not easily available. Doppler echocardiography is widely used in out-patients. Therefore we tried to assess which of the echocardiographically derived parameters are the most useful in PH diagnosis.

This study evaluated the value of echocardiography for the estimation of resting and exercise hemodynamics in SSc patients. Usefulness of echo Doppler estimation of right ventricular systolic

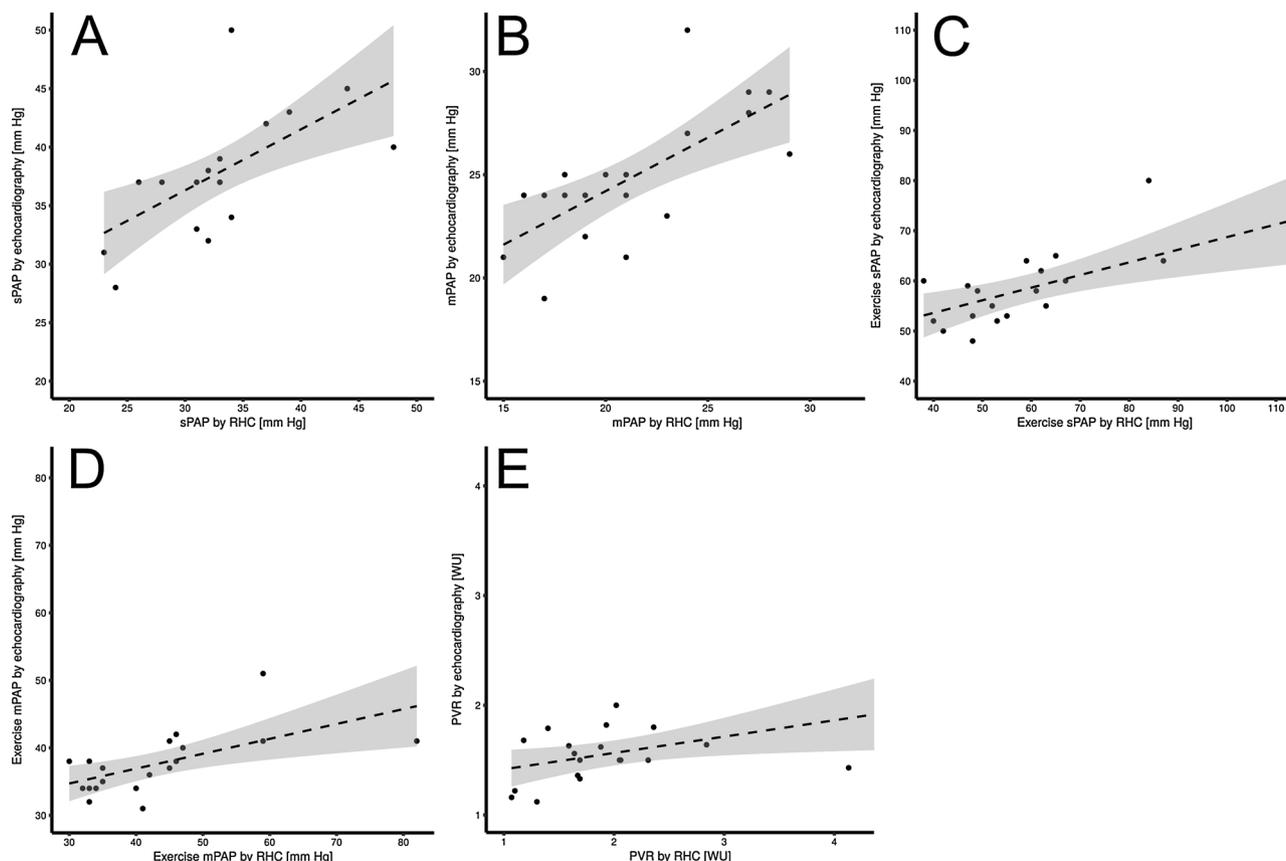
**Table 3**  
Comparison of echocardiographic and invasive hemodynamic parameters in 20 SSc patients.

Parameter	Echocardiography mean value ± SD	Catheterization mean value ± SD	Correlation 95% CI, p	Bland-Altman analysis Bias ± SD [LLoA with 95% CI and ULoA with 95%CI]
sPAP (mmHg)	38.0 ± 5.2	33.2 ± 6.6	0.66 (0.31-0.85) p = 0.001*	4.8 ± 5.1 [-5.1 (-9.2 to -0.1), 14.7 (10.6 to 18.8)]
mPAP (mmHg)	24.8 ± 3.1	21.2 ± 4.2	0.7 (0.37-0.87) p = 0.001*	3.7 ± 3.0 [-2.2 (-4.6 to 0.2), 9.5 (7.1 to 11.9)]
exercise sPAP (mmHg)	58.9 ± 7.3	59.7 ± 18.8	0.68 (0.33-0.87) p = 0.001#	-1.2 ± 15.1 [-30.8 (-43.5 to -18.1), 28.5 (15.8 to 41.2)]
exercise mPAP (mmHg)	37.8 ± 4.5	43.0 ± 12.7	0.67 (0.31-0.86) p = 0.002#	-5.4 ± 10.5 [-26.0 (-34.9 to -17.2), 15.2 (6.4 to 24.0)]
PVR (WU)	1.57 ± 0.27	2.02 ± 0.90	0.49 (0.06-0.77) p = 0.027*	-0.45 ± 0.80 [-2.0 (-1.4 to -2.7), 1.1 (0.5 to 1.8)]

SD – standard deviation; CI – confidence interval; LLoA – lower limit of agreement; ULoA – upper limit of agreement; \* – Pearson correlation coefficient; # – Spearman correlation coefficient; sPAP – systolic pulmonary artery pressure; mPAP – mean pulmonary artery pressure; PVR – pulmonary vascular resistance; WU – Wood units.

pressure (RVSP) is well known since Curie et al. [14] and Berger et al. [15] demonstrated good correlation between echocardiographic estimates and directly measured pressures. Resting RVSP remains the most commonly used echo Doppler parameter in routine clinical practices including screening and monitoring PH patients. There are a lot of data confirming its utility in SSc population [16,17]. Denton et al. [18] revealed in 33 SSc patients that sPAP obtained by Doppler echocardiography correlated highly with the value received at RHC ( $r = 0.83$ ,  $p < 0.001$ ). In our study, we confirmed a good correlation of sPAP

obtained by echocardiography and RHC (0.66,  $p = 0.001$ ), however, 3 of 20 patients (15%) pressures were overestimated (by 12, 11, and 26 mmHg, respectively). In routine daily practice clinicians should be aware that in some cases echocardiographic measurements may overestimate sPAP, but this parameter seems to be the most frequently used for screening SSc patients. However, PH has been defined as an increase in  $mPAP \geq 25$  mmHg at rest as assessed by RHC [3]. It is uncertain whether echocardiography can reliably estimate mPAP. Theoretically, the calculation of mPAP from PA systolic pressure is possible. Chempla



**Fig. 1.** Relationship between echocardiographic and invasive measurements with fitted linear regression line (95% confidence intervals were marked). Panel A – sPAP, panel B – mPAP, panel C – exercise sPAP, panel D – exercise mPAP, panel E – PVR.

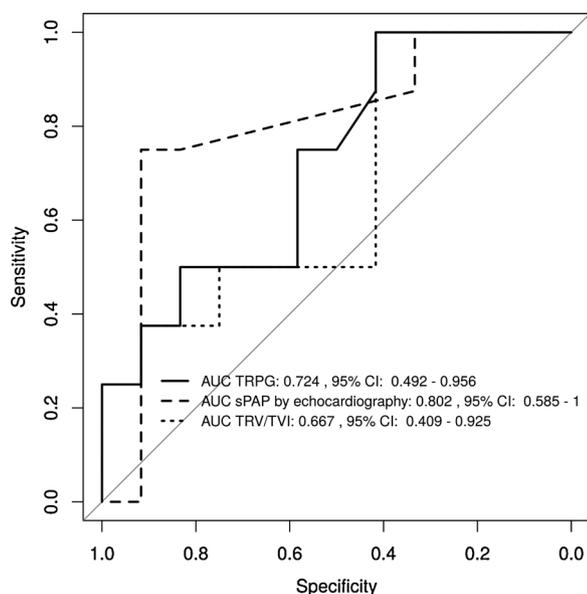


Fig. 2. AUC for RV/RA gradient, sPAP, TRV/TVI as predictors of PVR > 2 WU. AUC – area under curve; CI – confidence interval.

et al. [10] proposed a formula ( $mPAP = 0.61 \cdot PA \text{ systolic pressure} + 2 \text{ mm}$ ), the accuracy of which has been verified in PH patients. We confirmed that echo Doppler evaluation in SSc patients is a reliable method for estimation of mPAP and correlates significantly with RHC ( $r = 0.7$ ,  $p = 0.001$ ). It may be suitable in clinical practice for non-invasive evaluation of mPAP, but further studies are needed to confirm this apparent utility.

SSc patients often experience dyspnea with exercise. Alkotob et al. [19] and Mininni et al. [20] revealed that exercise-induced increases in TRPG on echocardiogram commonly occur in SSc, but RHC was not performed to confirm these findings. Steen et al. [12] evaluated 54 SSc patients and revealed an increase in exercise TRPG > 20 mmHg in 44% of them. PAH was confirmed by RHC in 81% of patients: 19% at rest and 62% with exercise. There are also new data that exercise testing can unmask right ventricular dysfunction in SSc patients with normal resting pulmonary pressure [21]. In all of our SSc patients the EPAPR was confirmed invasively. Both exercise sPAP and mPAP correlated significantly with RHC ( $0.68$ ,  $p = 0.001$  and  $0.67$ ,  $p = 0.002$ , respectively), although 2 of 20 patients (10%) exercise sPAP pressures were overestimated in echo examination by more than 10 mmHg of the value from RHC (22 and 12 mmHg, respectively) and 2 patients (10%) pressures were underestimated (23 and 22 mmHg, respectively). Exercise mPAP was underestimated in 3 (15%) of 20 patients (10, 18 and 21 mmHg, respectively). Echocardiographic evaluation of exercise sPAP and mPAP is promising and may be useful in selected SSc patients - especially with normal sPAP at rest and dyspnea with exercise - but further studies are needed.

PVR is a critical parameter in the assessment and treatment of patients with PH, regardless of etiology. Abbas et al. [11] have demonstrated Doppler ability to estimate PVR noninvasively. They have shown that a simple noninvasive Doppler calculation such as  $TRV/VTI_{RVOT}$  correlates well with invasive PVR measurement. Vlahos et al. [22] in a group of 12 PH patients, revealed a significant correlation between echo Doppler derived PVR and PVR calculated invasively ( $r = 0.71$ ) but, in this population, mean PVR was rather high (18 WU). In a study published by Rajagopalan et al. [23], discussing 52 PH patients, significant correlation was demonstrated between  $TRV/VTI_{RVOT}$  and PVR by catheterization ( $r = 0.73$ ,  $p < 0.001$ ). However, Bland-Altman analysis showed that agreement between PVR determined by echocardiography and invasive PVR was poor [23]. According to recent recommendations from the European Association of Cardiovascular

Imaging and the American Society of Echocardiography regarding the clinical use of stress echocardiography [24], assessment of exercise PVR using the equation of Abbas et al. [11] could be considered in patients with increased risk of PAH development. In a recently published paper, Rudski et al. [25] highlight that EDE is a useful noninvasive method for screening high risk populations, but further prospective studies are warranted to evaluate its sensitivity and specificity.

In our SSc patients we found a significant, but rather weak, correlation between echocardiographic and invasive PVR ( $r = 0.49$ ,  $p = 0.027$ ). We also performed ROC analysis to predict  $PVR > 2 \text{ WU}$ . Our results highlight that sPAP has the highest AUC (0.802, 95% CI 0.585–1). These findings warrant further investigation in SSc population patients. However, we think that noninvasive assessment of pulmonary pressures in SSc patients will be suitable to improve their daily care.

#### 4.1. Study limitations

Echocardiography and RHC were not performed simultaneously (within 6 weeks), but patients were in stable condition and after echo examination no changes in therapy were made. Moreover, slightly different exercise protocols (standard treadmill for echocardiography assessment and cycle ergometer in the supine position for RHC) may have influenced the results. In addition, the relatively small number of patients is a potential limitation. Our study group included patients with rather low values of PVR so it was not representative of the general PAH population.

## 5. Conclusion

Doppler resting and exercise echocardiography may provide a reliable, noninvasive method for determining resting and exercise systolic PAP, mean PAP and PVR in SSc patients although it may underestimate or overestimate these values in some individuals. Doppler echocardiography does not replace cardiac catheterization for definite hemodynamic assessment of suspected PH.

#### Conflict of interest

The authors declare no conflict of interest.

#### Financial disclosure

The authors have no funding to disclose.

#### The author contribution

Study design: Michał Ciużyński, Piotr Bienias, Piotr Pruszczyk.

Data collection: Michał Ciużyński, Piotr Bienias, Anna Chrzanowska, Katarzyna Ciesielska, Maria Siwicka, Iwona Dudzik-Niewiadomska, Katarzyna Kurnicka, Justyna Domienik-Karłowicz, Agnieszka Kalińska-Bienias, Marcin Kurzyna.

Statistical analysis: Piotr Sobieraj, Michał Ciużyński.

Data interpretation: Michał Ciużyński, Piotr Bienias, Piotr Pruszczyk.

Manuscript preparation: Michał Ciużyński, Piotr Sobieraj, Piotr Bienias, Piotr Pruszczyk.

Literature search: Michał Ciużyński, Piotr Bienias.

Funds collection: n/a.

## References

- [1] Mukerjee D, St GD, Coleiro B, Knight C, Denton CP, Davar J, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;62(11):1088–93.
- [2] Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, et al.

- Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010;138(6):1383–94.
- [3] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European society of cardiology (ESC) and the European respiratory society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2015;37(1):67–119. 2016.
- [4] D'Alto M, Ghio S, D'Andrea A, Pazzano AS, Argiento P, Camporotondo R, et al. Inappropriate exercise-induced increase in pulmonary artery pressure in patients with systemic sclerosis. *Heart* 2011;97(2):112–7.
- [5] Czurzyński M, Bienias P, Irzyk K, Kostrubiec M, Bartoszewicz Z, Siwicka M, et al. Exaggerated increase of exercise-induced pulmonary artery pressure in systemic sclerosis patients predominantly results from left ventricular diastolic dysfunction. *Clin Res Cardiol* 2013;102(11):813–20.
- [6] Kovacs G, Herve P, Barbera JA, Chaouat A, Chemla D, Condliffe R, et al. An official European Respiratory Society statement: pulmonary haemodynamics during exercise. *Eur Respir J* 2017;50(5).
- [7] van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. Classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013;72(11):1747–55. 2013.
- [8] Nagueh SF, Smiseth OA, Appleton CP, Byrd 3rd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging* 2016;17(12):1321–60.
- [9] Brennan JM, Blair JE, Goonewardena S, Ronan A, Shah D, Vasaiwala S, et al. Reappraisal of the use of inferior vena cava for estimating right atrial pressure. *J Am Soc Echocardiogr* 2007;20(7):857–61.
- [10] Chemla D, Castelain V, Humbert M, Hebert JL, Simonneau G, Lecarpentier Y, et al. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest* 2004;126(4):1313–7.
- [11] Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM, Vlahos AP, et al. Noninvasive assessment of pulmonary vascular resistance by Doppler echocardiography. *J Am Soc Echocardiogr* 2013;26(10):1170–7. <https://doi.org/10.1016/j.echo.2013.06.003>.
- [12] Steen V, Chou M, Shanmugam V, Mathias M, Kuru T, Morrissey R. Exercise-induced pulmonary arterial hypertension in patients with systemic sclerosis. *Chest* 2008;134(1):146–51.
- [13] Czurzyński M, Bienias P, Irzyk K, Rymarczyk Z, Kostrubiec M, Szewczyk A, et al. Usefulness of echocardiography in the identification of an excessive increase in pulmonary arterial pressure in patients with systemic sclerosis. *Kardiologia Pol* 2011;69(1):9–15.
- [14] Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD, et al. Continuous wave Doppler determination of right ventricular pressure: a simultaneous Doppler-catheterization study in 127 patients. *J Am Coll Cardiol* 1985;6(4):750–6.
- [15] Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol* 1985;6(2):359–65.
- [16] Wigley FM, Lima JA, Mayes M, McLain D, Chapin JL, Ward-Able C. The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary health care level of community-based rheumatologists (the UNCOVER study). *Arthritis Rheum* 2005;52(7):2125–32.
- [17] Pope JE, Lee P, Baron M, Dunne J, Smith D, Docherty PS, et al. Prevalence of elevated pulmonary arterial pressures measured by echocardiography in a multi-center study of patients with systemic sclerosis. *J Rheumatol* 2005;32(7):1273–8.
- [18] Denton CP, Cailles JB, Phillips GD, Wells AU, Black CM, Bois RM. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. *Br J Rheumatol* 1997;36(2):239–43.
- [19] Alkotob ML, Soltani P, Sheatt MA, Katsenos MC, Rothfield N, Hager WD, et al. Reduced exercise capacity and stress-induced pulmonary hypertension in patients with scleroderma. *Chest* 2006;130(1):176–81.
- [20] Mininni S, Diricatti G, Vono MC, Giglioli C, Margheri M, Olivo G, et al. Noninvasive evaluation of right ventricle systolic pressure during dynamic exercise by saline-enhanced Doppler echocardiography in progressive systemic sclerosis. *Angiology* 1996;47(5):467–74.
- [21] Chia EM, Lau EM, Xuan W, Celermajer DS, Thomas L. Exercise testing can unmask right ventricular dysfunction in systemic sclerosis patients with normal resting pulmonary artery pressure. *Int J Cardiol* 2016;204:179–86.
- [22] Vlahos AP, Feinstein JA, Schiller NB, Silverman NH. Extension of Doppler-derived echocardiographic measures of pulmonary vascular resistance to patients with moderate or severe pulmonary vascular disease. *J Am Soc Echocardiogr* 2008;21(6):711–4. <https://doi.org/10.1016/j.echo.2007.10.004>.
- [23] Rajagopalan N, Simon MA, Suffoletto MS, Shah H, Edelman K, Mathier MA, et al. Noninvasive estimation of pulmonary vascular resistance in pulmonary hypertension. *Echocardiography* 2009;26(5):489–94.
- [24] Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2016;17(11):1191–229.
- [25] Rudski LG, Gargani L, Armstrong WF, Lancellotti P, Lester SJ, Grunig E, et al. Stressing the cardiopulmonary vascular system: the role of echocardiography. *J Am Soc Echocardiogr* 2018;31(5). 527-50 e11.