Research Article

Echocardiographic Test and the Early Detection of Systolic Failure in Systemic Sclerosis Patients: Strain and Strain Rate Echocardiography

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Abstract

Background: Pulmonary arterial hypertension (PAH) is a leading cause of death in systemic sclerosis (SSc) patients. Early detection of systolic failure in SSc patients will facilitate early treatment and improve the survival rate of these patients.

Objectives: In this study, besides studying the RV function in SSC patients, attempts have been made to find a new possible noninvasive echocardiographic test for early diagnosis of systolic failure as a PAH complication.

Methods: 30 patients with at least a 2-year history of diffuse SSc confirmed by an expert rheumatologist were enrolled in this study. All the patients underwent transthoracic echocardiography by an echocardiologist. Fractional area change (FAC) of the right ventricle (RV), tricuspid annular plane systolic excursion (TAPSE), RV lateral wall strain and strain rate (Base, Mid, Apex), RV-EDD and RV pressure with respect to inferior vena cava (IVC) diameter as well as Left Ventricle's Ejection Fraction (LVEF) were evaluated.

Results: The prevalence rate of PAH was reported 36.6% in this study. There was no significant relationship between LVEF and RV parameters. LVEF was found to be significantly higher in women whereas RV strain turned out to be higher in men. Besides, there was a significant relation between pulmonary arterial pressure (PAP) and Basal (P = 0.03), mid RV strain (P = 0.002), RV strain rate (P = 0.001) and RV diameter (P = 0.02). Also, an inverse relation was observed between RV systolic (P = 0.01) and diastolic functions (P = 0.007) with PAP. In addition, no significant relationship was found between LVEF and body mass index (BMI) and RV parameters (P > 0.05). Moreover, Apical RV strain and LVEF were found to be higher in males and females respectively. Furthermore, a significant relationship was found between RV strain and age (P = 0.027). Finally, the results did not show any relationship between RV systolic and diastolic functions and gender.

Conclusions: This paper states the likely advantages of strain and strain rate echocardiography in identifying patients with more diffused and severe SSc and the need for further longitudinal studies based on the mentioned method for early diagnosis of myocardial impairment.

Keywords: Scleroderma, Systemic Sclerosis (SSc), Pulmonary Arterial Hypertension (PAH), Right Ventricle (RV) function, Systolic Failure, Tissue Doppler Imaging (TDI), Strain and Strain Rate Echocardiography

1. Background

Progressive systemic sclerosis disease (PSS) is a serious connective tissue disorder which is divided into two limited and diffuse types (1). The skin/tissue form is commonly observed in the limited type with the lung interstitial fibrosis and pulmonary hypertension not being rare in these patients. Further, vascular symptoms such as severe Raynaud phenomenon and widespread telangiectasia are also common in these patients (1-3), which makes it an important complication of systemic sclerosis (SSC) (4). It is difficult to present an accurate measurement for prevalence of this

form; however, it is estimated it encompasses 15% of all SSc cases. In comparison to the diffuse form, pulmonary arterial hypertension (PAH) is more common in the limited form, which is mainly caused by the lung interstitial tissue fibrosis.

The clinical symptoms at the early stages of the disease are often negligible but as the disease progresses, advanced symptoms such as shortness of breath and severe pulmonary hypertension (PAH) arise in patients (4). The survival period for the untreated patients with PAH has been reported 2 to 3 years. In other words, if the disease is not diagnosed at early stages, it will lead to a high mor-

tality rate due to the right ventricular failure as the main cause of death.

Therefore, the use of a noninvasive diagnostic technique and the early diagnosis of this disorder would be beneficial to the SSc patients as it can help adopt timely therapeutic interventions and prevent the emergence of right ventricular dysfunction symptoms. In this regard, this paper presents an echocardiographic study with special emphasis on the new echocardiographic parameters of right ventricular function and pulmonary arterial pressure level. Also, the literature calls for more widespread investigation of the RV function in SSc patients (5).

According to the literature, these techniques as an isovolumetric acceleration have been shown to be useful for diagnosis of right ventricular systolic failure and pulmonary hypertension (6), increased right atrial, right ventricular and pulmonary artery pressure in right heart catheterization (4, 7) DETECT algorithm (8), low carbon monoxide diffusing capacity and high speed of tricuspid valve reflex (9), as well as elevated RV Tei-index (10). In the same vein, an earlier technique developed for the diagnosis of left and right ventricular diastolic failure is decreased exercise capacity (11). In addition, another study has shown that pulsed Doppler imaging and strain rate imaging are significantly useful for the assessment of RV function in SSc patients (12).

2. Objectives

In this study, besides studying the RV function in SSc patients, attempts have been made to find a new possible noninvasive echocardiographic test for the early diagnosis of systolic failure as a PAH complication.

3. Methods

In this study, the RV function was evaluated in accordance with the latest ASE/AHA guidelines, all parameters related to RV longitudinal and radial functions were determined, all data were measured and digitally recorded by an echocardiologist for further analysis.

In addition, in this study Scleroderma was diagnosed as a rheumatic disease characterized by an increase in fibrosis level of connective tissue all over the body. Moreover, the pulmonary arterial hypertension was found to be characterized by an intrinsic pressure inside pulmonary arteries which was equal or greater than 35 mmhg. Also, the condition of pulmonary arterial walls, which were under the influence of right ventricular function, was analyzed.

All the patients with advanced types of SSc who were referred to the rheumatic research center as well as the cardiovascular research center of Mashhad University of Medical Sciences included in this study.

The inclusion criteria allowed for the participation of every patient with diffuse systemic sclerosis. On the contrary, the exclusion criteria were unwillingness of the patient to undertake echocardiography, unstable conditions, arrhythmia, a history of pulmonary diseases or any valvular heart diseases, history of PCI, CABG or documented IHD and a history of rheumatic valvular disease or any proved cardiac diseases.

In this study, the relationship between echocardiographic parameters of global and regional right ventricular function and pulmonary arterial pressure in SSc patients was evaluated. Moreover, this study evaluated the relationship between the changes of TDI, strain/ strain rate parameters and the pulmonary arterial pressure level, and also the relationship between right ventricular function parameters, measured by TDI technique, and age and sex.

In the study conducted by Vonk (10), the correlation coefficient between PAP and Tei index of right ventricle was reported 0.46 (r = 0.46). Hence, the initial sample size (n = 19) was increased to 30 due to parametric methods and analysis of the relation between other variables.

The main data gathering method was a field study supplemented by observation and checklists.

Out of the patients referred to the clinic, 30 individuals with advanced systemic scelerosis who had at least a 2-year history of the disease were included in this study following the confirmation of the disease by an expert rheumatologist. All the patients were allowed to participate in the transthoracic echocardiographic study after signing the informed consent form. The echocardiographic study was performed with an ultrasound machine (Vivid 7, GE Medical Systems, Horten, Norway 2008) with a 2.5 - 3.5 -MHz ultrasound probe in accordance with the ASE/AHA guidelines while monitoring by an expert echocardiologist. All the standard parameters were measured and recorded for further analysis.

The measured parameters included right ventricular fractional area change (RV FAC) (percentage), tricuspid annular plane systolic excursion (TAPSE) (cm), right ventricular lateral wall, tissue doppler imaging (TDI) velocities (S, E and A) (cm/s), right ventricle strain (Base, Mid, Apex) (percentage), basal and mid- RV strain rate, RV end diastolic diameter (RV-EDD) (cm), right ventricle pressure with respect to IVC diameter in mmhg, and LVEF (percentage), age (year, month and day), gender (F/M), height (cm), weight (Kg), and also period of hospitalization (day).

PAP, RV fractional area change, TAPSE, RV dimensions (Basal RV diameter/RV1, Mid RV diameter/RV2, Base to Apex

length/RV3) and also RV outflow tract (RVOT) diameters (above aortic valve/RVOT1, above pulmonic valve/RVOT2) were classified as normal, mildly abnormal, moderately abnormal and severely abnormal, as shown in Table 1.

The statistical analysis of the data was performed by the SPSS software. In this study, the significant interval was assumed 95%. In addition, the chi-square test and t-test were used to compare different groups, also Pearson and spearman correlations for analyzing quantitative variables.

4. Results

In this study, 80% of the patients were female and 20% were male. The age range of females was 14 to 67 with a mean age of 40 ± 10. For males, the age range was 18 to 75 with a mean age of 46 ± 11.

The relationship between pulmonary arterial pressure (PAP) and each of the right ventricular (RV) function parameters including RV longitudinal function parameter at Base (or BASAL RV strain), RV longitudinal function parameter at Mid (or MID RV strain), RV longitudinal function parameter at apex (or APICAL RV strain), the speed of RV longitudinal function change (or the RV strain rate), RV longitudinal function parameter using M mode technique of Tricuspid valve, RV transverse diameter from a 4- chamber view and tissue velocities, in SSc patients was investigated and the correlation coefficient and significance levels were computed.

The Pearson and spearman correlations revealed an inverse and significant relationship between basal RV strain (P = 0.003 cc = -0.572), mid RV strain (P = 0.002, cc = -0.590) RV strain rate (P = 0.0 and cc = -0.677) and PAP. In addition, a direct and significant correlation was found between RV transverse diameter (P = 0.02 and cc = 0.4) and PAP.

Additionally, the relationship between PAP and RV systolic and diastolic functions in SSc patients were investigated and the correlation coefficient and significant levels were calculated. According to Pearson and Spearman correlations, RV systolic function (P = 0.0 and cc = -0.694) and RV diastolic function (P = 0.007 and cc = -0.480) were in an inverse and significant relationship with PAP.

Likewise, only a direct and significant relationship was found between mid RV strain and age (P = 0.027 and cc = 0.451). Similarly, there was only a direct and significant relationship between apical RV strain and gender (P = 0.021 and cc = 0.513).

The RV systolic function was observed to be normal in 100% of males while this figure was only 80% in females. 10% of females had mildly reduced RV systolic function while approximately 3% had severely reduced RV systolic function. (P > 0.05)

As shown in Table 2, results of the independent t-test indicate comparison of the variables in SSc patients with gender. They were significantly higher in males than females whereas the LV EF was significantly higher in females (P = 0.025).

Furthermore, given that PAP was normal in 63.4% of the SSc patients, 36.6% of them were estimated to have PAH (27.3% were cases with mild PAH, 45.4% with moderate PAH and 27.3% with severe PAH).

In addition, analysis of RV transverse diameter (from the 4-chamber view) in SSc patients revealed a diameter between 2 - 2.9 cm in 23% of the patients, diameter between 3 - 3.9 cm In 50% and diameter between 4 - 4.9% in 18%. Meanwhile, the minimum and maximum diameters were 2.3 cm and 4.8 cm respectively.

Moreover, the value of mid RV strain in all the patients was reported as follows: 8% were between -49 and -40, 12% between -39 and -30, 40% between -29 and -20, and 18% between -19 and -10. Here, the minimum and maximum values were -41S% and -16% (Figure 1).
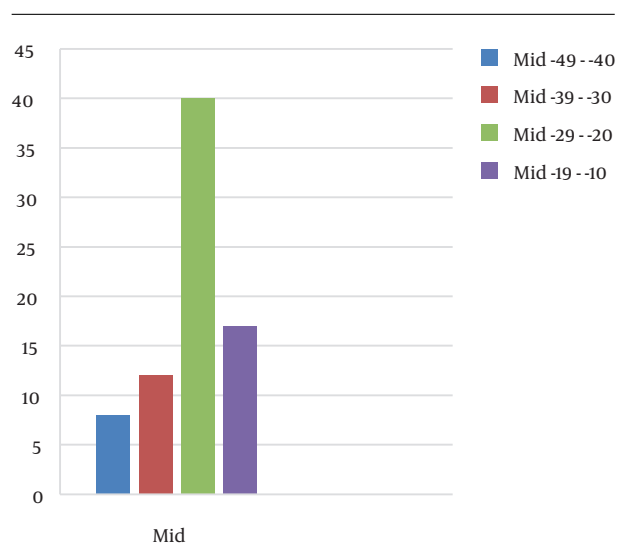

Figure 1. RV Longitudinal Function Index at Mid (MID RV Strain)

Also, in 50% of the patients, RV longitudinal function parameter at Base was between -29 and -20 while in approximately 8% it was between -39 and -30. However, the lowest and highest values in all the patients were reported -31 and -12 respectively (Figure 2).

The results suggested that most patients had normal contraction power (Figure 3).

We also investigated the relationship between the height and RV function parameter in SSc patients. The Pearson and spearman correlations showed a direct and significant relationship between apical RV strain and height (P =

Table 1. Classifying Values (13, 14)

	Normal	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
PAP, mmHg	18 - 34	35 - 44	45 - 64	$\geq$ 65
RV fractional area change, cm^2	32 - 60	25 - 31	18 - 24	$\leq$ 17
TAPSE, cm	1.6 - 2	1.3 - 1.59	1 - 1.29	< 1
RV dimensions, cm^2				
RV1	2 - 2.8	2.9 - 3.3	3.4 - 3.8	$\geq$ 3.9
RV2	2.7 - 3.3	3.4 - 3.7	3.8 - 4.1	$\geq$ 4.2
RV3	7.1	8 - 8.5	8.6 - 9.1	$\geq$ 9.2
RVOT diameters, cm				
RVOT1	2.5 - 2.9	3 - 3.2	3.3 - 3.5	$\geq$3.6
RVOT2	1.7 - 2.3	2.4 - 2.7	2.8 - 3.1	$\geq$3.2

Table 2. Results of Comparison Between the Variables in SSc Patients With Gender

Variable	P Value
Weight	0.004
RV strain apical	0.01
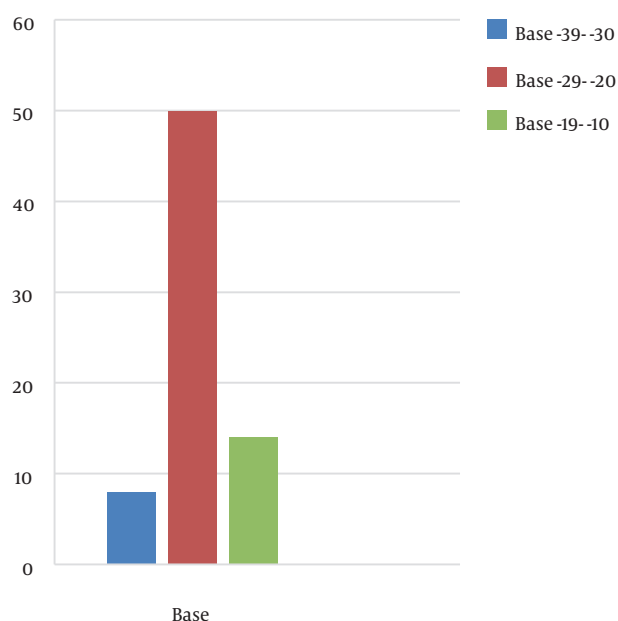
Figure 2. RV Longitudinal Function Index at Base (Basal RV Strain)

Figure 3. Left Ventricular Ejection Fraction

0.015 and cc = 0.536).

Moreover, Pearson and Spearman correlations suggested the absence of any significant relations between RV function parameters and weight, BMI and LVEF (P = 0.04).
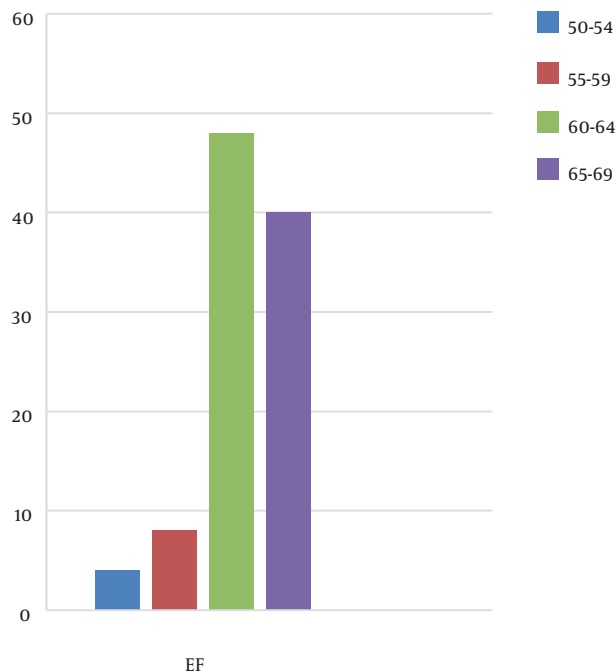
5. Discussion

In this study, consistent with the study carried out by Kanski et al. (15), women outnumbered men (9 males and 18 females), though the average age of the subjects in that study was relatively higher than that of patients in our research (57 years old). In the same vein, in the study by Jansa et al., females outnumbered males (82.3%) and the average age of the subjects was similar to our study (53.8 years old) (16). The number of SSc patients was evaluated in line with

the reference books and the age range of this disease ([2](#)).

In the study by Andrea et al. patients with both diffused (11 patients) and limited (12 patients) types of SSc disease were examined ([12](#)). In our study; however, only the diffused type of the disease was considered, as recommended by the previous studies.

According to the results, considering that RV strain, RV strain rate and RV systolic function are in an inverse and significant relation with PAP, it can be concluded that there is a direct and significant relationship between the RV strain and RV strain rate parameters and the RV systolic function of the heart. Hence, these two new noninvasive echocardiographic parameters (Tissue Doppler-based strain and strain rate) can be used for the early diagnosis of RV systolic failure in SSc patients. In other words, it can help hinder the progress of pulmonary arterial pressure level in SSc patients. Considering the fact that PAH is the leading cause of death in SSc patients, this will reduce mortality in these cases. Additionally, in this way PAH symptoms and shortness of breath can be mitigated in SSc patients. However, it will reduce health care costs for these patients. The RV diastolic function was also found to be correlated with the PAP level so that an increase in PAP level deteriorates the diastolic function and reduces RV free wall tissue Doppler E/A ratio.

The possibility of RV failure diagnosis in 3D echocardiography and 2D-3D speckle-tracking imaging has been reported by Vitarelli et al. ([17](#)). In addition, Stergiopoulos et al. have shown that speckle-tracking echocardiography (STE) is a sensitive tool for RV dysfunction assessment in acute pulmonary embolism patients ([18](#)). Chow et al. found that 2D global longitudinal strain and strain rate are potentially useful indices for the assessment of RV function ([19](#)). However, TDI strain and strain rate assessment offer a convenient and cheaper alternative to the study of RV function in SSc patients.

In addition, according to Utsunomiya et al. RV strain has been shown to help analyze the RV function in patients with chronic pulmonary hypertension ([20](#)). Similar to our study, it proves the usefulness of RV strain for the assessment of RV, but, unlike our study, it is limited to the patients with chronic pulmonary hypertension. Moreover, regarding the study conducted by Filusch et al. RV strain has been depicted to aid the analysis of the RV function in patients with idiopathic pulmonary hypertension ([21](#)). Again, consistent with our study, it proves the usefulness of RV strain for the assessment of RV, but unlike our study, it was restricted to the patients with idiopathic pulmonary hypertension.

Comparing to the findings of an Italian cohort study ([22](#)) and a Czech Republic cohort study ([16](#)), the prevalence of PAH in SSc patients (36.6%) was found to be much higher

in our study. In addition, another study found that such prevalence was even higher (64% and 61%) in patients with tricuspid valve failure ([4](#)). In the study conducted by Vonk et al. ([10](#)) the prevalence rate was significantly high (80%) though the prevalence of PAH in the study of Coghlan et al. was relatively lower (19%) than the rate reported in our study ([9](#)). In the same manner, this figure was reported to be low by Acosta Colman et al. (20.5%) in comparison to our study ([11](#)).

In addition, a direct and significant relationship was found between MID RV strain and age. Moreover, apical RV strain and gender were observed to be in a direct and significant relationship. In other words, strain at Apex is higher among male SSc patients. On the other hand, the LV EF was observed to be significantly higher in females SSc patients.

Also, the results suggest that among 36.6% of the patients with PAH, 27.3% had a mild PAH, 45.4% a moderate PAH and 27.3% had a severe PAH. Since this distribution is normal, it can be concluded that PAH commonly emerges in a moderate form and then grows gradually.

Moreover, the prevalence of RV longitudinal function parameters in patients was as follows: the mid RV strain was -29 to -20 in 40%, -40 to -49 in 8%, -39 to -30 in 12%, and -19 to -10 in 18% of the patients. In other words, the RV strain at mid was normally distributed in SSc patients, with its peak between -29 and -20.

Likewise, the basal RV strain was -29 to -20 in 50%, and -39 to -30 in 8% of the patients. In other words, the RV strain at Base followed the normal distribution which peaked at the range of -29 to -20.

LVEF was normal in most SSc patients. That is, RV failure was more prevalent than LV failure in SSc patients. Besides, the statistical tests did not show any significant relationship between RV function parameters and LVEF.

Similarly, the results did not show any significant relationship between RV function parameters and BMI and weight. Nonetheless, a direct and significant relationship was found between RV longitudinal function parameter and height.

5.1. Conclusions

In summary, the prevalence rate of PAH in SSc patients was reported 36.6% in our study. In addition, this study demonstrated a direct and significant relationship between the RV transverse diameter (from the 4-chamber view) and PAP. Moreover, PAP was found to be in an inverse and significant relation with the basal and mid RV strain and velocity change of the RV longitudinal function.

Also, the LV EF in women was found to be greater than men, though height, weight and apical RV strain were significantly higher in men. Additionally, RV strain at Mid was

found to be in a significant and direct relationship with age while RV strain at apex was significantly and directly related to height.

Moreover, according to results, RV function indexes were not in any significant relationship with weight, BMI and LVEF.

In addition to the normal systolic function of the right ventricle in our study (according to the TAPSE, S wave and FAC standards), the strain and strain rate parameters were in an inverse and significant relationship with PAP level.

In conclusion, strain and strain rate imaging present a novel, convenient and useful method for early diagnosis of subclinical systolic failure in SSc patients with pulmonary artery hypertension.

This paper states the likely advantages of strain and strain rate echocardiography in identifying patients with more diffused and severe SSc and the need for further longitudinal studies based on the mentioned method for early diagnosis of myocardial impairment.

Acknowledgments

Footnote

Authors' Contribution: Zahra Rezai Yazdi, Afsoon Fazlinezhad, Fariba Alizadeh Sani, Leila Bigdelu: doing and supervision of the study; Afsoon Fazlinezhad, G. Tabatabaei Yazdi: writing the manuscript; Azra Izanloo: editing the manuscript.

References

1. Fauci AS, Langford C. Harrison's rheumatology. McGraw Hill Professional; 2010.
2. Isselbacher KJ, Adams RD. Harison's Principles of internal medicine. New York: Mc Graw-Hill Book Company; 2010.
3. Braunwald E, Bonow RO. Braunwald's heart disease. Elsevier Saunders; 2012.
4. Denton CP, Cailes 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. [PubMed: 9133938].
5. Vonk Noordegraaf A, Naeije R. Right ventricular function in scleroderma-related pulmonary hypertension. *Rheumatology (Oxford).* 2008;**47 Suppl 5**:v42–3. doi: 10.1093/rheumatology/ken284. [PubMed: 18784141].
6. Schattke S, Knebel F, Grohmann A, Dreger H, Kmezik F, Riemekasten G, et al. Early right ventricular systolic dysfunction in patients with systemic sclerosis without pulmonary hypertension: a Doppler Tissue and Speckle Tracking echocardiography study. *Cardiovasc Ultrasound.* 2010;**8**:3. doi: 10.1186/1476-7120-8-3. [PubMed: 20096122].
7. Codullo V, Caporali R, Cuomo G, Ghio S, D'Alto M, Fusetti C, et al. Stress Doppler echocardiography in systemic sclerosis: evidence for a role in the prediction of pulmonary hypertension. *Arthritis Rheum.* 2013;**65**(9):2403–11. doi: 10.1002/art.38043. [PubMed: 23754201].
8. Ciurzynski M, Bienias P, Lichodziejewska B, Szewczyk A, Glinska-Wielochowska M, Jankowski K, et al. Assessment of left and right ventricular diastolic function in patients with systemic sclerosis. *Kardiol Pol.* 2008;**66**(3):269–76. [PubMed: 18393114] discussion 277-8.
9. Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis.* 2014;**73**(7):1340–9. doi: 10.1136/annrheumdis-2013-203301. [PubMed: 23687283].
10. Vonk MC, Sander MH, van den Hoogen FH, van Riel PL, Verheugt FW, van Dijk AP. Right ventricle Tei-index: a tool to increase the accuracy of non-invasive detection of pulmonary arterial hypertension in connective tissue diseases. *Eur J Echocardiogr.* 2007;**8**(5):317–21. doi: 10.1016/j.euje.2006.06.002. [PubMed: 16846757].
11. Acosta Colman MI, Avila Pedretti G, Acosta ME, Simeon Aznar CP, Fonollosa Pla V, Villardel Torres M. Can we predict the severity of pulmonary hypertension in patients with scleroderma?. *Reumatol Clin.* 2012;**8**(5):259–62. doi: 10.1016/j.reuma.2012.03.007. [PubMed: 22658662].
12. D'Andrea A, Stisi S, Bellissimo S, Vigorito F, Scotto di Uccio F, Tozzi N, et al. Early impairment of myocardial function in systemic sclerosis: non-invasive assessment by Doppler myocardial and strain rate imaging. *Eur J Echocardiogr.* 2005;**6**(6):407–18. doi: 10.1016/j.euje.2005.01.002. [PubMed: 16293527].
13. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;**7**(2):79–108. doi: 10.1016/j.euje.2005.12.014. [PubMed: 16458610].
14. Weyman AE. Principles and practice of echocardiography. USA: Lea and Febiger; 1994.
15. Kanski M, Arheden H, Wuttge DM, Bozovic G, Hesselstrand R, Ugander M. Pulmonary blood volume indexed to lung volume is reduced in newly diagnosed systemic sclerosis compared to normals–a prospective clinical cardiovascular magnetic resonance study addressing pulmonary vascular changes. *J Cardiovasc Magn Reson.* 2013;**15**:86. doi: 10.1186/1532-429X-15-86. [PubMed: 24066703].
16. Jansa P, Becvar R, Ambroz D, Palecek T, Tomcik M, Skacelova S, et al. Pulmonary arterial hypertension associated with systemic sclerosis in the Czech Republic. *Clin Rheumatol.* 2012;**31**(3):557–61. doi: 10.1007/s10067-011-1896-x. [PubMed: 22105781].
17. Vitarelli A, Mangieri E, Terzano C, Gaudio C, Salsano F, Rosato E, et al. Three-dimensional echocardiography and 2D-3D speckle-tracking imaging in chronic pulmonary hypertension: diagnostic accuracy in detecting hemodynamic signs of right ventricular (RV) failure. *J Am Heart Assoc.* 2015;**4**(3):e001584. doi: 10.1161/JAHA.114.001584. [PubMed: 25792128].
18. Stergiopoulos K, Bahrainy S, Strachan P, Kort S. Right ventricular strain rate predicts clinical outcomes in patients with acute pulmonary embolism. *Acute Card Care.* 2011;**13**(3):181–8. doi: 10.3109/17482941.2011.606468. [PubMed: 21877878].
19. Chow PC, Liang XC, Cheung EW, Lam WW, Cheung YF. New two-dimensional global longitudinal strain and strain rate imaging for assessment of systemic right ventricular function. *Heart.* 2008;**94**(7):855–9. doi: 10.1136/hrt.2007.131862. [PubMed: 18230639].
20. Utsunomiya H, Nakatani S, Okada T, Kanzaki H, Kyotani S, Nakanishi N, et al. A simple method to predict impaired right ventricular performance and disease severity in chronic pulmonary hypertension using strain rate imaging. *Int J Cardiol.* 2011;**147**(1):88–94. doi: 10.1016/j.ijcard.2009.08.009. [PubMed: 19747741].
21. Filusch A, Mereles D, Gruenig E, Buss S, Katus HA, Meyer FJ. Strain and strain rate echocardiography for evaluation of right ventricular dysfunction in patients with idiopathic pulmonary arterial hypertension. *Clin Res Cardiol.* 2010;**99**(8):491–8. doi: 10.1007/s00392-010-0147-5. [PubMed: 20352437].

22. Iudici M, Codullo V, Giuggioli D, Riccieri V, Cuomo G, Breda S, et al. Pulmonary hypertension in systemic sclerosis: prevalence, incidence and predictive factors in a large multicentric Italian cohort. *Clin Exp Rheumatol.* 2013;**31**(2 Suppl 76):31–6. [PubMed: 23910607].