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Abnormal pulmonary artery systolic pressure response after exercise in systemic sclerosis patients

A PRISMA-compliant meta-analysis

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Abstract

Background: Pulmonary artery systolic pressure (PASP) is an important parameter for detecting pulmonary arterial hypertension (PAH). The difference between rest PASP and post-exercise PASP (ΔPASP) may play a role in predicting and screening resting PAH. The aim of this study is to analyze ΔPASP in systemic sclerosis (SSc) patients with PAH or non-PAH and suggest a cutoff value of ΔPASP for detection of PAH.

Methods: PubMed, Embase, and Web of Science were searched for relevant publications up to July 7, 2018. Characteristics of control, no PAH, exercise-induced PAH (EIPH) and PAH subgroups in SSc patients were extracted. R 3.5.0 with the "meta" package was used to conduct this meta-analysis.

Results: Twelve articles involving 1279 patients were included in this study. The subgroups meta-analysis showed pooled mean ΔPASP in different subgroups: control group (8.6 mmHg, 95% CI: 6.9–10.5), no PAH group (12.2 mmHg, 95% CI: 11.2–13.2), EIPH group (26.0 mmHg, 95% CI: 24.2–27.7) and PAH group (36.2 mmHg, 95% CI: 29.7–42.7).

Conclusion: Combining the results of our study with the previous studies, an abnormal increase in PASP after exercise could indicate the development of PAH in SSc patients. In addition, if ΔPASP>29 mmHg, a high suspicion of PAH should be raised.

Abbreviations: ΔPASP = mean difference between rest PASP and post-exercise PASP, CIs = confidence intervals, EIPH = exercise-induced PAH, MDs = mean differences, N = sample size, NOS = Newcastle-Ottawa Scale, PAH = pulmonary arterial hypertension, PASP = pulmonary artery systolic pressure, RHC = right heart catheterization, SDE = stress Doppler echocardiography, SSc = systemic sclerosis, TDE = transthoracic Doppler echocardiography at rest, TRV = peak tricuspid regurgitation velocity.

Keywords: meta-analysis, pulmonary arterial hypertension, pulmonary artery systolic pressure, stress Doppler echocardiography, systemic sclerosis

1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease, and it is prone to develop pulmonary arterial hypertension (PAH).[1] PAH, as one of the most common causes of death in SSc patients,[2] is associated with a worse prognosis.[3–6] The French ItinérAIR-Sclérodermie study reported that more than 80% of SSc patients with PAH complications were in World Health Organization functional class II–IV.[7] Three-year survival rate for SSc patients with untreated PAH (56%) was considerably lower than those patients without PAH (91%).[8] Correct and prompt treatment is crucial to improve the prognosis.[9] Currently, several PAH-targeted drugs could be used for these patients.[10,11,12] Therefore, early detection or diagnosis of PAH is essential for SSc patients with this severe disorder.

PAH is defined as the mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg obtained by right heart catheterization (RHC), and this remains the reference standard for diagnosing PAH. However, RHC is an invasive examination with recognized

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risk and complications,[13–15] as it requires exposure to ionizing radiation and contrast. Guidelines suggest transthoracic Doppler echocardiography (TDE) as the routinely initial screening test for PAH.[9]

Echocardiography at rest is a frequently used noninvasive method for PAH detection. It provides peak tricuspid regurgitation velocity (TRV), and an estimate of pulmonary artery systolic pressure (PASP). With RHC as a reference standard, the ESC/ERS guidelines[9] has recommended a TRV of at least 3.4 m/s or PASP of 50 mmHg as a cutoff value for conducting RHC to diagnose or exclude PAH in SSc patients. However, accuracy and reliability of TDE at rest has recently been questioned. In the multicenter DETECT study,[16] echocardiography using these cutoff values alone did not reliably detect early stage of PAH in patients with SSc. This study reported only 30% of 84 SSc patients with PAH had a TRV of at least 3.4 m/s. Moreover, in patients with advanced pulmonary disease, TDE also showed inaccuracy.[17]

Previous studies reported that, some SSc patients with or without clinical sign of PAH could have an inappropriate increase in echocardiography-estimated PASP under exercise.[18,19] Moreover, these patients presented a high risk of developing a manifest PAH within 1 to 3 years, and had poor prognosis.[20] Thus, stress Doppler echocardiography (SDE) may be a reliable method for identifying SSc patients with PAH at an early-stage.[21] Because of this, we speculated that difference between rest PASP and post-exercise PASP (ΔPASP) may be an effective parameter in predicting and detecting early PAH. However, the cutoff value of ΔPASP for screening PAH is still unclear,[9] and all relevant studies did not comprehensively analyze ΔPASP in SSc patients at different pathological stages. The aim of this meta-analysis is to clarify the change of PASP during exercise in SSc patients with or without PAH, and suggest a cutoff value for predicting and screening PAH.

2. Method

2.1. Publication search and selection criteria

PubMed, Embase, and Web of Science were consulted. The following search terms were applied using conjunctions in all document databases: "pulmonary hypertension", "right heart catheterization", "echocardiography" and "systemic sclerosis." Syntax for PubMed searches was as follows: "pulmonary hypertension" AND "right heart catheterization" AND "echocardiography" AND "systemic sclerosis". Articles published up to July 7, 2018, were included in the primary search. Studies in the primary search were excluded if any of the following items were present:

1. PASP estimated by echocardiography was not given.
2. Study was not regarding about SSc patients.
3. Sample size of a study group was less than 10.
4. Abstract or conference paper.
5. Non-English literature.

Articles search and evaluation were conducted by 2 independent investigators, Song Yang and Jing Wu, who reached consensus at all items.

2.2. Data extraction

Two authors (Song Yang and Jing Wu) independently collected the relevant data. The following items were extracted from included articles: name of first author, year of publication, study design, country of origin, number of control and cases, number of male and female participants, average age, PASP estimated by rest and exercise echocardiography.

2.3. Patients

In the original research articles,[18,19,22–31] which were selected for this secondary research, patients were excluded if they had one or more of the following items: a previous diagnosis of PAH before the original study, resting PASP $\geq$ 50 mmHg by echocardiography, receiving any cardioactive medications, left heart disease, severe systemic hypertension, arrhythmias or palpitations, severe lung disease.

According to the results of estimated PASP by echocardiography and mPAP by RHC,[1,9,23,25,27–30] SSc patients were classified into 3 subgroups: no PAH group, exercise-induced PAH (EIPH) group, and PAH group. No PAH group were those with post-exercise PASP $<$ 50 mmHg and ΔPASP $<$ 20 mmHg. EIPH group were those with post-exercise PASP $\geq$ 50 mmHg or ΔPASP $\geq$ 20 mmHg. PAH group were those with mPAP $\geq$ 25 mmHg newly confirmed by RHC during the original research. Additionally, control subjects were patients without systemic sclerosis.

2.4. Quality assessment

Our meta-analysis included 12 cohort studies. Newcastle-Ottawa Scale (NOS) was used as a tool to evaluate the methodological quality of cohort study.[32] Details of this checklist can be acquired from Ref.[33] Newcastle-Ottawa Scale is a valid tool to evaluate quality of a cohort study.[34] The NOS checklist consists of 3 aspects: selection of study groups (4 items), comparability of study groups (1 item), and outcome of interest for cohort studies (three items).[33] If the answer to an item was "Yes", the item would be 1 point. If the answer to an item was "Unclear" or "No", the item would be "0 points". A study with a score of 5 or more was considered to be high quality.[35,36] Otherwise, the quality of a study with 0 to 4 points was considered to be low. The quality of each included study was evaluated independently by 2 physicians [Song Yang and Jing Wu]. Table 2 shows the methodological quality of each included article.

2.5. Ethical review

Ethical approval was not necessary in the present study because only published statistical data was used in the current meta-analysis, and no personal data of patients were used.

2.6. Statistical analysis

This meta-analysis using DerSimonian-Laird method was conducted to calculate the difference between post-exercise and rest PASP (ΔPASP) estimated by echocardiography. Moreover, random-effects model was used for data synthesis. Mean differences (MDs) and corresponding 95% credible confidence intervals (CIs) were reported as results. The weight for each study was calculated using inverse variance method. Heterogeneity was assessed with Cochran Q test and inconsistency index test (I^2 test).[37,38] The existence of heterogeneity was indicated by a P value of Cochran Q test $<$0.1, and an I^2 value $>$50%.[37,38] Publication bias in this study was evaluated using Egger test. A P

Table 1

Characteristics of the included studies.

Study*	Reference Number	Location	Stress Protocol	Subgroup	N	Males/Female	Age In Years	PASP At Rest	PASP After Exercise
Nagel, 2015	[22]	Germany	Ergometer	PAH	22	N.G.	67.6±8.8	52.0±18.0	83.9±18.9
Suzuki, 2013	[23]	Japan	Master	Control	37	5/32	59±5.8	22.2±4.7	31.0±8.4
				EIPH	37	6/31	56.0±12.6	36.4±6.6	58.8±10.8
				PAH	15	3/12	58±14.8	41.6±7.4	80.2±14.3
Chia, 2016	[24]	Australia	Treadmill	Control	50	17/33	52.9±9.2	22.7±6.9	29.3±11.8
				no PAH	25	7/18	53.0±10.2	27.8±5.4	42.8±11.5
D'Alto, 2011	[18]	Italy	Ergometer	no PAH	172	17/155	51.86±21.5	26.2±5.3	36.9±8.7
Voilliot, 2014	[25]	Belgium	Ergometer	no PAH	24	9/15	48±11	21±5	36±8
				EIPH	21	2/19	62±12	29±6	58±9
Pignone, 2007	[26]	Italy	Ergometer	EIPH	18	N.G.	50.36±16.07	21.2±2.9	48.8±4.5
Ciurzyński, 2011	[27]	Poland	Treadmill	no PAH	67	3/64	56.9±17.1	26.9±7.6	40.3±14.1
Suzuki 2015	[28]	Japan	Master	no PAH	361	31/326	53.8±15.3	25.7±5.0	38.3±7.7
				EIPH	133	18/115	63.4±12.0	35.6±7.2	60.2±11.1
Kovacs, 2010	[19]	Austria	Ergometer	EIPH	26	N.G.	58±9	27±5	55±10
Voilliot, 2016	[29]	Belgium	Ergometer	EIPH	11	4/7	60±14	30±4	60±12
Takai, 2015	[30]	Japan	Master	Control	30	5/25	55±7.7	21.9±4.7	31.6±7.3
				no PAH	123	12/111	53.1±13.1	25.4±4.1	36.9±6.8
				EIPH	97	21/76	61.4±11.3	36.2±7.2	60.6±9.8
Collins, 2006	[31]	Australia	Treadmill	no PAH	10	0/10	52.1±8.3	21.2±6.6	36.5±15.4

* first author and publication year; N: sample size of each study group; PASP: systolic pulmonary arterial pressure; Ergometer, bicycle ergometry test in a semi-recumbent or supine position; Master, the Master two-step test; Treadmill, treadmill exercise testing; N.G., not given.

value less than .05 indicated that publication bias existed. Moreover, heterogeneity and publication bias of PAH group was not discussed due to it involving only 2 study groups. R 3.3.3 with the "meta" package was used to perform the meta-analysis.

3. Results

After a systematic literature search, 28 potentially relevant studies from a total of 648 articles were assessed for further evaluation. Finally, 12 publications [N=1279] were selected for this meta-analysis.[18,19,22–31] The process of selecting studies is shown in Figure 1. Among 1279 subjects within the included studies, 117 patients from 3 articles were assigned to the control group,[23,24,30] 782 patients from 7 articles were assigned to the no PAH group,[18,24,25,27,28,30,31] 343 patients from 7 articles were assigned to the EIPH group,[19,23,25,26,28,29,30] and 37 patients from 2 articles were assigned to the PAH group.[22,23]Table 1 summarizes characteristics of the studies.

3.1. Quantitative synthesis and heterogeneity assessment

The meta-analysis for ΔPASP subgroup showed that pooled MDs for each group were completely different. They were as follows: control group (8.6 mmHg, 95% CI: 6.9–10.5), no PAH group (12.2 mmHg, 95% CI: 11.2–13.2), EIPH group (26.0 mmHg, 95% CI: 24.2–27.7) and PAH group (36.2 mmHg, 95% CI: 29.7–42.7). Moreover, heterogeneity of the pooled overall ΔPASP was considerable among all the included studies (Cochran Q test, $P<.01$; I^2: 96.3%, 95% CI: 95.3–97.2%). The subgroup study suggests low heterogeneity in the no PAH ($I^2=36.1\%$) and EIPH groups ($I^2=46.1\%$), and no heterogeneity in the control group. Thus, the present study suggests different subgroups yield different ΔPASP. The forest plot of this meta-analysis is shown in Figure 2.

3.2. Quality of reporting and publication bias

All the 12 included studies were cohort studies published between 2006 and 2016. NOS scores are all over 5 points, as listed in Table 2, which suggests the reliability of our results. The Egger test for the control, no PAH and EIPH group was associated with P values of .21, .31 and .34, respectively, suggesting low likelihood of publication bias.

4. Discussion

In this meta-analysis, we summarized ΔPASP in different subgroups of systemic sclerosis patients. Our results suggest that ΔPASP could reflect different stages of pulmonary vascular disorders in SSc patients. Moreover, to the best of our knowledge, our meta-analysis is the first study that systemically evaluated ΔPASP in SSc patients in different pathological stages.

The results of this meta-analysis demonstrated that each group may have a different ΔPASP estimated by echocardiography: control (8.6 mmHg, 95% CI: 6.9–10.5), no PAH (12.2 mmHg, 95% CI: 11.2–13.2), EIPH (26.0 mmHg, 95% CI: 24.2–27.7) and PAH group (36.2 mmHg, 95% CI: 29.7–42.7). Hence, the limits of ΔPASP in different subgroups could provide cutoff values for screening and predicting early PAH in SSc patients.

Stress Doppler echocardiography (SDE) is an effective tool in screening for PAH.[22,23] Nagel et al[22] and Suzuki et al[23] reported sensitivity and specificity based on different post-exercise PASP cutoff values of at least 45 mmHg and at least 69.6 mmHg. Such values were 95.2/84.9% [N=76], and 93/90% [N=52], respectively. Compared with SDE, transthoracic Doppler echocardiography (TDE) at rest is not accurate and reliable for screening pulmonary hypertension in systemic sclerosis patients. Denton et al[39] described comparatively low sensitivity and specificity values of 90% and 75% [N=33], with a cutoff value of PASP at rest 30 mmHg. Condliffe et al[40] described echocardiography at rest that revealed a sensitivity of

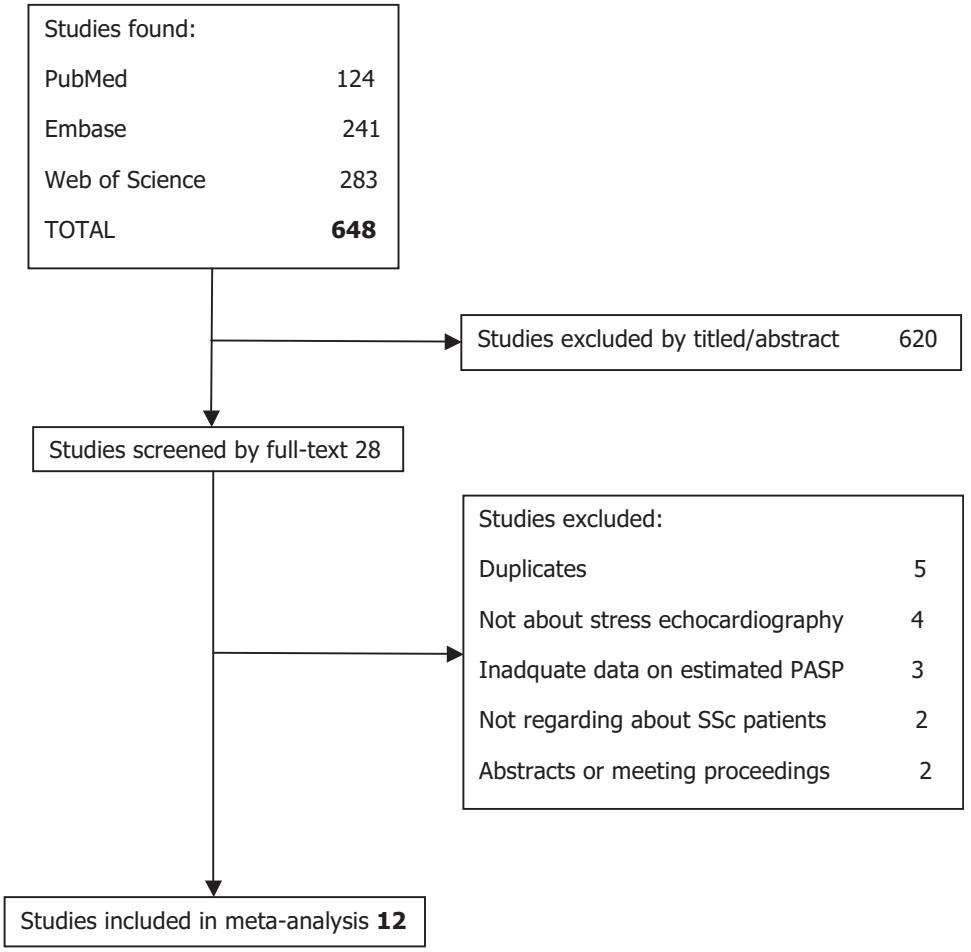

Figure 1. Study selection flowchart.

79% in detecting PAH and a specificity of 80% [N=89] when a cutoff value of PASP of at least 40 mmHg was used. Schreiber et al[41] described a sensitivity of 90.1% and a specificity of 29.2% [N=129], when mPAP (25 mmHg) at rest obtained by TDE was used for detecting PAH. Castillo et al[42] described that when the DETECT algorithm is applied, sensitivity was 100% and specificity was 42.9% [N=63]. Therefore, SDE has an advantage over TDE in detecting PAH. In contrast to post-exercise PASP, ΔPASP can directly reflect the change of PASP during exercise. We inferred that ΔPASP is more accurate than post-exercise PASP for the detection of PAH at an early stage.

Table 2

Methodological quality assessment.

Study	Reference Number	Study Design	Quality Score	Overall Methodological Quality
Nagel, 2015	[22]	Cohort study	6	high
Suzuki, 2013	[23]	Cohort study	6	high
Chia, 2016	[24]	Cohort study	6	high
D'Alto, 2011	[18]	Cohort study	6	high
Voilliot 2014	[25]	Cohort study	6	high
Pignone, 2007	[26]	Cohort study	6	high
Ciurzyński, 2011	[27]	Cohort study	7	high
Suzuki, 2015	[28]	Cohort study	7	high
Kovacs, 2010	[19]	Cohort study	7	high
Voilliot, 2016	[29]	Cohort study	8	high
Takai, 2015	[30]	Cohort study	7	high
Collins, 2006	[31]	Cohort study	7	high

The term "exercise-induced PAH" (EIPH) has been reported as a preclinic asymptomatic phase of resting PAH in SSc patients.[28,29,43] Stress echocardiography is considered to be an effective tool in predicting the development of PAH at rest in SSc patients.[29,43] Voilliot et al[29] reported 11 (64.7%) of 17 SSc patients with exercise PASP > 50 mmHg developed PAH during follow-up (25 ± 15 months). Codullo et al[43] described that ΔPASP > 18 mmHg could be used as a cutoff value with a sensitivity of 50% and specificity of 90% [N=170] for predicting the development of PH during follow-up (3.5 ± 0.2 years). Additionally, Yagi et al[44] reported bosentan ameliorated an EIPH patient with no PAH-related symptom and ΔPASP > 30 mmHg. Consequently, EIPH is a major predictive factor for onset of resting PAH in SSc patients, and it may provide evidence for bosentan therapy in future.

PAH in SSc patients is mainly caused by pulmonary arteriopathy,[45] which is secondary to systemic sclerosis. Pulmonary arteriopathy is related to an increase in pulmonary vascular resistance (PVR).[45,46] A rise in PVR can lead to an abnormal increase in PASP induced by exercise.[47] Consequently, ΔPASP in

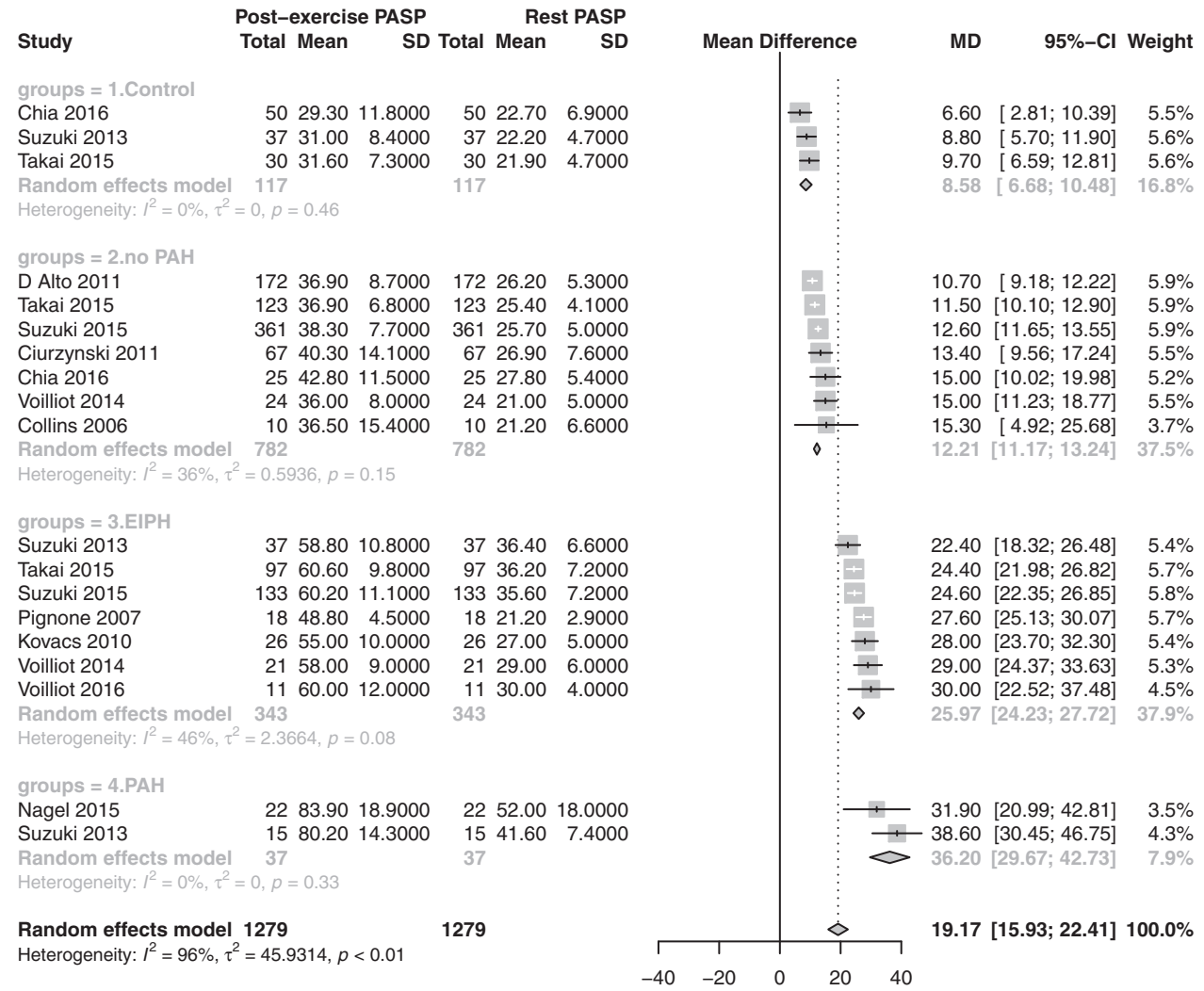

Figure 2. Forest plot of the mean difference (MD) between rest PASP and post-exercise PASP in SSc patients. CI = confidence interval, PASP = pulmonary artery systolic pressure.

SSc patients increases as the disease progresses. This is in accordance with results of this study.

Based on our results and relevant studies, we suggest that a SSc patient with ΔPASP > 24 mmHg should have regular follow-ups every 3 to 6 months as recommended by the guideline;[9] when ΔPASP is more than 29 mmHg, there should be a high degree of suspicion for PAH, and such patient should be advised to have right heart catheterization for pulmonary vascular hemodynamics assessment. However, further investigation is required to clarify validity and efficacy of these results. Moreover, a large-scale prospective study is also needed to confirm whether SSc patients with ΔPASP > 30 mmHg could benefit from bosentan therapy for PAH treatment.

5. Limitations

Some limitations of this study should be highlighted. Due to limited reported data, several hemodynamic parameters (pulmonary vascular resistance, right ventricular contractile reserve, left ventricular systolic, diastolic dysfunction, etc.) could not be analyzed. Due to lack of evidence supporting the accuracy of ΔPASP in detecting PAH, the validity and role of ΔPASP is unclear. Moreover, the stress protocols of exercise electrocardiography test are different in different study groups.

6. Future directions

The accuracy and validity of ΔPASP for the detection of early PAH should be discussed in a further large-scale prospective study. Additionally, further research is required for comparing accuracy and risk between different exercise tests (such as ergometer exercise test, treadmill exercise test and master's 2-step exercise test) in detecting PAH.

7. Conclusion

ΔPASP in SSc patients may increase as their illness progresses, and it may also be a useful parameter for predicting and detecting early PAH. Further research is required to assess both its validity and efficacy.

Author contributions

All authors approved publication, and the role of each author as below:

Song Yang contributed to drafting this work, writing and revising this paper, searching relevant literatures, assessing the quality of each included article, data extraction, analysis and interpretation of data for this work.

Jing Wu contributed to searching relevant literatures, assessing the quality of each included studies, and revising this work

Si Lei, Rong Song and Ye-yu Cai contributed to revising this work.

Shang-jie Wu contributed to revising this work, and providing the outline, conception and direction of this study.

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