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Original article

Incidence of pulmonary hypertension in patients with Takayasu's arteritis: A transthoracic echocardiographic evaluation

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ABSTRACT

Aim: In this study, we aim to evaluate the incidence of pulmonary hypertension (PH) using transthoracic echocardiography (TTE) in Takayasu arteritis (TA) patients.
Methods: Thirty-four outpatient Takayasu arteritis patients underwent transthoracic echocardiography (TTE) following the ESC-ERS guidelines. A tricuspid regurgitation velocity (TRV) greater than 3.4 m/s indicated a high probability of pulmonary hypertension (PH). The patients were categorized based on their New York Heart Association (NYHA) functional class (FC) and symptomatic status. All patients underwent a six-minute walk test (6MWT) and pulmonary function tests (PFT).
Results: A total of 30 patients with a mean age of 40 ± 9.3 years were enrolled in the study. Among these patients, four (13.3%) were met the criteria for high probability of PH (TRV: 4 ± 0.92), with a mean systolic pulmonary artery pressure (SPAP) of 76.7 ± 37. There were no significant differences in terms of age, disease duration, and erythrocyte sedimentation rate (ESR) between the PH and non-PH groups. However, there was a significant difference in tricuspid annular plane systolic excursion TAPSE/SPAP ratio between NYHA functional class (FC) Group 1 and Group 2 (1.2 ± 0.16 vs 0.83 ± 0.24, $p = 0.018$). Additionally, TAPSE showed a correlation with forced expiratory volume in the first second/forced vital capacity (FEV_1/FVC) ($r = 0.446$, $p = 0.043$).
Conclusions: Pulmonary hypertension is a not uncommon complication in Takayasu arteritis (13.3% vs 11.3% in the literature). Considering the symptoms and functional capacity, lowering the threshold for initiating transthoracic echocardiography (TTE) evaluation may be beneficial for early risk stratification of pulmonary hypertension in patients with Takayasu arteritis.

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Incidencia de hipertensión pulmonar en pacientes con arteritis de Takayasu: una evaluación ecocardiográfica transtorácica

Palabras clave:
Hipertensión pulmonar
Arteritis de Takayasu

RESUMEN

Objetivo: En este estudio, pretendemos evaluar la incidencia de hipertensión pulmonar (HP) mediante ecocardiografía transtorácica (ETT) en los pacientes con arteritis de Takayasu (AT).

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Arteria pulmonar
Ecocardiografía
Pruebas de función pulmonar
Prueba de la marcha de 6 min

Métodos: Se realizó una ecocardiografía transtorácica (ETT) a 34 pacientes ambulatorios con AT siguiendo las directrices de la ESC-ERS. Una velocidad de regurgitación tricuspídea (VTR) superior a 3,4 m/s indicaba una alta probabilidad de HP. Los pacientes se clasificaron en función de su clase funcional (CF) de la New York Heart Association (NYHA), y se sometieron a una prueba de marcha de 6 min (6MWT) y a pruebas de función pulmonar (PFP).
Resultados: Un total de 30 pacientes con una edad media de 40 ± 9,3 años fueron incluidos en el estudio. Entre estos pacientes, 4 (13,3%) cumplían los criterios de alta probabilidad de HP (TRV: 4 ± 0,92), con una presión arterial pulmonar sistólica (PAPS) media de 76,7 ± 37. No hubo diferencias significativas en cuanto a la edad, la duración de la enfermedad y la velocidad de sedimentación globular (VSG). No hubo diferencias significativas en cuanto a edad, duración de la enfermedad y velocidad de sedimentación globular (VSG) entre los grupos con y sin HP. Sin embargo, se observó una diferencia significativa en el desplazamiento sistólico del plano del anillo tricuspídeo en la relación TAPSE/SPAP entre los grupos 1 y 2 de CF de la NYHA (1,2 ± 0,16 frente a 0,83 ± 0,24; p = 0,018).
Conclusiones: La HP es una complicación no infrecuente en la AT (13,3 frente al 11,3% en la bibliografía). La reducción del umbral para iniciar la evaluación mediante ETT puede ser beneficiosa para la estratificación precoz del riesgo.
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Introduction

Takayasu arteritis (TA) is a chronic vasculitis of unknown etiology predominantly affecting young females. Besides the aorta and its branches as classic sites of disease, TA may also involve the pulmonary arteries. The vascular inflammation in TA can result in arterial wall thickening, stenosis/occlusion, and aneurysmal dilatation. Diagnosis of pulmonary artery involvement (PAI) can be delayed due to non-specific presenting symptoms. It leads to significant vascular damage at the time of diagnosis and increase in serious cardiopulmonary sequels, particularly pulmonary hypertension (PH). These complications have an adverse impact on the prognosis and risk of invasive intervention.[1–3]

In recent years, with advances in imaging modalities, PAI in TA patients has been a concerning issue.[4] The frequency of the pulmonary arteritis varies greatly among studies and has been reported to range generally between 5.7% and 26% based on the recent studies,[2] and up to 56% in autopsy reports.[5,6]

During the course of Takayasu arteritis, pulmonary hypertension may develop in 0–20% of patients secondary to pulmonary arteritis (PA) (group 4 PH) or left heart disease (group 2 PH).[2] Pulmonary hypertension due to pulmonary arteritis is a form of pre-capillary PH characterized by increased vascular resistance; it is hemodynamically distinguished from a PH developed primarily due to left heart disease (LHD) in TA.[7] Transthoracic echocardiography (TTE) is a valuable non-invasive tool in detecting early PH signs via measuring cardiac hemodynamic.[8] Given the insidious nature of pulmonary artery involvement and subsequent pulmonary hypertension, early diagnosis and intervention before the occurring of irreversible sequels is critical. This study aimed to investigate, the incidence of pulmonary hypertension in Takayasu arteritis patients using the echocardiography findings relating to the functional status of patients.

Methods

This study was conducted from January 2016 to December 2019, and the protocol for the research and data collection was approved by the Institutional Ethics Committee.

Takayasu arteritis patients who were being followed at rheumatology outpatient clinics of two general academic hospitals were enrolled. The medical records were reviewed. All patients fulfilled the 1990 criteria of the American College of Rheumatology for the diagnostic classification of Takayasu arteritis.[9] The patients with incomplete records, lost follow-up and those with prior known history or risk factors for PH were excluded. Other vasculitis with large vessel involvement and those with prominent pulmonary involvement (e.g., antineutrophil cytoplasmic antibody associated-vasculitis-associated vasculitis and etc.) have been excluded during initial diagnostic process and patients' follow-up in the clinic.

All patients' records were reviewed according to their demographic data, comorbidities, disease duration, and symptoms (Table 1). The patients were invited to perform TTE and pulmonary function tests and six-minutes walking test (6MWT). All patients were classified according to New York Heart Association (NYHA) functional class I–IV.

All echocardiography were performed by two expert echocardiologists. Erythrocyte sedimentation rate (ESR) test, as an index of disease activity based on Kerr criteria, was also performed within the days of echocardiographic assessment. The echocardiographic measurements were performed according to the recent European Society of Cardiology (ESC)/European Respiratory Society (ERS) criteria.[8] We used Doppler measurement for estimation of peak tricuspid regurgitation velocity (TRV) as the main variable for categorizing probability of PH (not simply the estimated sPAP) as follows: (1) TRV > 3.4 m/s or 2.9–3.4 in the presence echocardiographic signs suggesting PH from at least two different categories was considered high probability PH, (2) TRV of 2.9 to 3.4 or greater than 2.8 was considered intermediate, and (3) TRV ≤ 2.8 or not measurable was considered low probability.

TAPSE was measured on M-mode images as the difference in RV basal motion from peak systole to end-diastole. sPAP was calculated from peak tricuspidal jet velocity using the simplified Bernoulli equation by adding the estimated right atrial pressure (eRAP) to the systolic *trans*-tricuspid pressure gradient. RA pressure (RAP) was estimated based on the inferior vena cava (IVC) end-expiratory diameter and collapsibility at the end-inspiratory phase, as recommended.[8] The TAPSE/sPAP ratio was then calculated for all patients. Patients with high probability of PH scheduled to undergo Computed tomography pulmonary angiography (CTPA) to exclude other causes of pulmonary arterial lesions especially chronic thromboembolic pulmonary hypertension (CTEPH). If clinically indicated, right heart catheterization (RHC) on resting was undertaken to confirm the presence and classification of PH (group II or IV): mean pulmonary arterial pressure (mPAP) ≥ 20 mm Hg at rest and pulmonary vascular resistance ≥ 3 Wood units and pulmonary artery wedge pressure ≤ 15 mm Hg were defined as pre-capillary PH.[7]

Table 1
Demographic, echocardiography, and pulmonary volumes between patients with and without PH.

Characteristics	Total (*N* = 30) (Median, IQR)	Non-PH (*N* = 26) (Median, IQR)	Probable PH (*N* = 4) (Median, IQR)	*p* value
Age (years)	39.5 (32.7–47.2)	39 (32.5–49.2)	39 (32.5–43)	NS
BMI	25.4 (21.9–27.9)	25.4 (21.7–27.9)	26.2 (22.5–30.1)	NS
Disease duration (months)	96 (66.5–145)	103 (49.5–145.5)	96 (87–150)	NS
ESR, mm/h	30 (19–43.5)	29 (14.5–43.5)	33 (23.25–47.45)	NS
NYHA function class, *N* (%)				
FC 1	20 (66.6)	20 (66.6)	–	
FC 2	6 (20)	6 (20)	–	
FC 3	4 (13.3)	–		
FC 4	–	–	–	
6 minute walking test (6MWT) (m)	410 (377–482)	435 (397–492)	300 (280–357)	**0.003**
Echocardiographic index				
TAPSE (mm)	20 (16.5–22.75)	21 (19.25–23)	13.5 (12.25–14.75)	**0.004**
TRV (m/s)	2.29 (1.9–2.69)	2.1 (1.8–2.3)	3.9 (3.2–4.9)	**0.002**
PH probability, *n* (%)				
Low		25 (83.3)		
Intermediate		1 (3.3)		
High		4 (13.3)		
SPAP (mmHg)	26 (20–34)	23 (19–28)	67 (49–116)	**0.002**
LVEF (%)	56 (52–60)	56 (52–60)	56.5 (28.7–61)	NS
Pulmonary function index				
FEV_1 (%)	88 (75–95.5)	90 (80–96)	67.5 (64–76)	**0.015**
FEV_1/FVC (%)	91 (87–101)	91.5 (86.2–102.5)	90.1 (88.2–95.5)	NS
Diffusion capacity for carbon monoxide (DLCO) (%)	83.5 (71.5–96.2)	85 (77.5–97)	62 (44.75–66)	**0.003**
FVC/DLCO (%)	105.8 (94–120)	103.3 (92.9–119)	130.5 (112.12–130.5)	**0.032**
RV/TLC (%)	133 (113–141.5)	129.5 (113–140)	145 (115.5–159.5)	NS
Residual volume (%)	122 (107.5–146)	122 (107.5–136)	134.5 (105.7–161)	NS
Total lung capacity (%)	95.5 (88.5–114)	95 (88.5–103.8)	100 (85.25–109)	NS

BMI: body mass index; ESR: erythrocyte sedimentation rate; NYHA: New York Heart association, TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitant velocity; SPAP: systolic pulmonary artery pressure; LVEF: left ventricular ejection fraction; FEV_1: forced end expiratory volume in one second; FVC; forced vital capacity, RV: residual volume; TLC: total lung capacity; DLCO: Diffusion Capacity for Carbon Monoxide; NS: non-significant.

Additionally, all patients underwent pulmonary function tests including measurement of dynamic lung volumes, residual volumes (RV), total lung capacity (TLC), and diffusing capacity of the lung for carbon monoxide (DLCO). The results of PFTs were used as an adjunct modality in order to assess cardiopulmonary symptoms such as dyspnea or cough in the patients and to investigate other possible parenchymal or airways causes contributing to increased systolic pulmonary artery pressure.

We conducted also a comprehensive review of the English language literature published in the Medline/PubMed and Scopus database since 1960 with the following keywords: “Takayasu Arteritis”, “Pulmonary Arteritis”, “pulmonary involvement”, and “Pulmonary Hypertension”. A total of 36 studies focusing on incidence of Takayasu arteritis and its pulmonary manifestations were included. We excluded: (1) studies without a clear data on both of PAI and PH frequencies, (2) Case reports including those which had reported the cases with an isolated pulmonary involvement, (3) the studies conducted in the same center during close period of times, and (4) studies without a clear data on symptomatic status of patients. A total of 11 studies were enrolled and summarized in Table 2.

Statistical analysis

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were used to summarize the data. The continuous data were expressed as the median and interquartile range (IQR, 25th and 75th percentiles). The categorical variables were presented as numbers and percentages. The Mann–Whitney *U* and Fisher tests were used to compare quantitative and categorical non-normally distributed variables, respectively. Kruskal–Wallis test was also used to compare variables difference among 3 group. Spearman coefficient was used to evaluate the linear correlation. A p-value < 0.05 was considered as statistically significant.

Results

From January 2016 to December 2019, the records of 34 patients with Takayasu arteritis were extracted. Four patients were excluded from the study; one with a trivial TR jet signal, two lost follow-ups, and one patient died due to septic shock. Finally, a total of 30 patients were enrolled. All patients were female (100%) with a mean age of 40 ± 9.3 years. The mean disease duration from diagnosis was 111 ± 67 months. Demographic and echocardiographic features of TA patients are summarized in Table 1. Four (13%) patients met the criteria for high probability of PH (TRV: 4 ± 0.92); the median systolic pulmonary artery pressure (SPAP) was 67 (76.7 ± 37) mmHg. There were no significant differences between TA patients with and without PH, in terms of age (38.2 ± 5.6 vs. 40.3 ± 9.8; $p = 0.64$), body mass index (BMI) (26.3 ± 3.9 vs. 25.1 ± 6.1; $p = 0.58$), and disease duration (111 ± 38.4 vs. 112 ± 70.8; $p = 0.76$). Regarding ESR level, there was no significant difference between the PH and non-PH group ($p = 0.57$), as well as, among group with impaired Function Class (FC 2 and 3) and those without limitation in activity (FC 1) ($p = 0.30$).

Out of all patients, six (20%) had respiratory symptoms: dyspnea in four patients (13%) and cough in three (10%) patients. Out of all patients, four patients were in NYHA FC 3 (13%) with a mean TRV: 3.9 m/s which all meet TTE criteria for PH; six patients (20%) were found to be in NYHA FC 2. Only one case with a TRV: 3.1 m/s and FC 2 was categorized in TTE as intermediate PH probability.

There were also significant differences among patient in FC 2 and FC 1 in term of BMI (26 ± 4.4 vs. 22.1 ± 3.1, $p = 0.045$), 6MWT

Table 2
Incidence of pulmonary involvement throughout different studies in Takayasu arteritis.[a]

Study, year	Ref.	Age	Country	Imaging	PH def. Defintion	Total	PAI	PH	Pulmonary symptom[b]
Lupi. 1975	[11]	14–42	Mexico	CA	*mPAP > 25*	22	11/22(50%)	6/22(27%)	None
Paul. 1999	[39]	45	France	CTA	–	41	22/41(53%)	5/41(12%)	11/41(26%)
Castellani. 2001	[40]	20–66	Italy	PS	*mPAP > 25*	18	10/18(55%)	2/18(11%)	None
Mekinian. 2012	[41]	36	France	PS	–	21	12/21(57%)	2/21(9%)	4/21(19%)
Brennan. 2016	[1]	31	America	Echo	*RVSP > 40*	92	9/45(20%)	7/60(11%)	24/45(53%)
Kalfa. 2018	[23]	42	Turkey	Echo	*TRV > 3.4 or sPAP > 40*	70	4/70(5%)	None	None
Sari. 2018	[34]	41	Turkey	Echo	*sPAP > 40*	64	12/64(18%)	7/64(11%)	2/64(3%)
Kong. 2020	[2]	35	Chinese	CTA+PS	*sPAP > 40*	216	56/216(26%)	34/216(15%)	51/216(23%)
He. 2020	[17]	38	Chinese	CTA/CA	*TRV > 3.4*	598	128/598(21%)	80/598(11%)	68/598(11%)
Mukoyama. 2020	[42]	54	Japan	CTA/MRA	*mPAP > 20*	166	24/166(14%)	4/166(2%)	19/166(11%)
Yazici. 2021	[21]	42	Turkey	CTA/PET-CT	–	319	18/319(5.6%)	33/307(10%)	82/319(25%)
							306/1580:**19.3%**	180/1583:**11.3%**	261/1580: **16.5%**

PS: pulmonary scintigraphy; CA: conventional angiography; DSA: digital subtraction angiography; CTA: computed tomographic angiography; MRA: magnetic resonance angiography; PET: positron emission tomography; PAI: pulmonary artery involvement; PH: pulmonary hypertension.

[a] The search strategy in Supplementary Fig. 1.

[b] Include dyspnea, hemoptysis, cough.

Table 3
Grouping of Takayasu arteritis patients based on NYHA functional class (FC).

ECHO. and PFTs	FC 1 ($n=20$)	FC 2 ($n=6$)	FC 3 ($n=4$)	p value
6MWT(m)	455 (410–507)	370 (347–410)	300 (280–357)	<0.000
TAPSE/sPAP (mm/mmHg)	1.2 (1.06–1.37)	0.83 (0.6–1.05)	0.19 (0.12–0.27)	0.001
TRV(m/s)	2.19 (1.8–2.3)	1.9 (1.8–2.5)	3.9 (3.2–4.9)	0.006
FEV_1(%)	92 (81–98)	86 (68–91)	67 (64–76)	0.017
DLCO (%)	86 (77–100)	84 (76–88)	62 (44–66)	0.005

6MWT: 6 minute walk test; NYHA: New York Heart association; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitant velocity; SPAP: systolic pulmonary artery pressure; FEV_1: forced end expiratory volume in one second; DLCO: diffusion capacity for carbon monoxide.

(375 ± 43 vs 462 ± 60, $p = 0.004$), TAPSE (24 ± 2.7vs. 20.3 ± 3.1, $p = 0.032$), respectively. TAPSE/SPAP had a meaningful difference between FC 1 and 2 (1.2 ± 0.16 vs 0.83 ± 0.24, $p = 0.018$). Moreover, among these 3 groups of FC, the meaningful differences in term of the echocardiography and PFTs index were observed (Table 3).

In Spearman rank test, TAPSE as an indicator of right ventricle overload was also correlated with FEV_1/FVC ($r = 0.446$, $p = 0.043$). TAPSE/SPAP was also correlated with vital capacity ($r = 0.458$, $p = 0.028$).

According to 6MWT, TA patients with <440 m (56%) compared to those with >440 m had lower FEV_1 ($p = 0.009$). Additionally 6MWT showed correlations with FEV_1 ($p = 0.003$, $r = 0.526$), DLCO ($p = 0.028$, $r = 0.41$) and tend to be correlated with TAPSE in Takayasu arteritis patients ($p = 0.057$, $r = 0.394$).

In the group with high-probability PH, no significant obstructive abnormality in PFT or cardiac valvular affection were found justifying the increased pulmonary pressure. Thus, the patients were classified under the group 4 pulmonary hypertension due to pulmonary arteritis.[7] RHC was only indicated in a 35-year-old patient with TRV of 4.3 m/s and a reduced ejection fraction (20%) which underwent RHC, in which mPAP was 46 mmHg, pulmonary vascular resistance (PVR) was 15.5 Wood Unit and pulmonary artery wedge pressure (PAWP) was 15 mmHg. This confirmed a diagnosis of a pre-capillary PH as the primary cause of systolic dysfunction. Because of normal PAWP, she was started on Bosentan 125 mg Bid.

None of the enrolled patients had a prior history of a significant pulmonary disease or on any pulmonary-related drugs. Based on PFTs, no significant obstruction was found. In our patients with high-Probability PH, the mean value of DLCO were 62% of predicted which is considered a mild decrease based on the severity classification. FEV_1% (71.5 ± 5.8 vs. 87.5 ± 13.3; $p = 0.015$) and DLCO (58.7 ± 13.3 vs. 88 ± 16.3; $p = 0.003$) were also significantly lower in the PH group.

Discussion

Pulmonary artery involvement in TA

The research by Nasu et al. (1963) was the first systematic series of autopsy in patients with a disorder known at the time as “pulseless disease”; the authors reported that pulmonary artery involvement had been found in more than 50% (12/21) of the patients.[10] Similar findings were noted in an angiographic study by Lupi (1975), highlighting the importance of evaluating pulmonary circulation in Takayasu arteritis.[11] Later, with introducing newer criteria, pulmonary artery involvement was established as the known finding in TA patients.[12,13]

A notable variation in frequency of pulmonary artery involvement is present throughout literature ranging from 0 to 86%; earlier studies using invasive modalities reported an average prevalence of 50%, mostly in Takayasu arteritis cases without respiratory symptoms (Table 2).[11,14–16] It is presumed that PAI prevalence may have been subject to selection bias throughout the literature where it has been specifically looked for. In a report by He et al., for suspected TA cases who underwent pulmonary vascular imaging, the incidence of PAI was 66%, while a prevalence of 21% was obtained in the total population.[17] Similarly, Gong et al. reported an incidence rate of 37% in TA patients with at least one respiratory symptom.[18] Other probability for this variation, including disease duration, different diagnostic criteria and the genetic/ethnic background of different vascular predilection may in part account for this variation.[19,20]

Pulmonary hypertension in TAs

The frequency of pulmonary hypertension in our study is comparable to a recent multicenter study on Takayasu arteritis cases in Turkey (10% vs. 13.3% in the current study).[21] The prevalence of Takayasu arteritis-associated pulmonary hypertension (TA-PH)

vary through the literature ranging between 0 and 20% (Table 2). In a review study by Toledano, a high incidence of PH was noted (42%), which is an unusually higher incidence than general findings throughout the literature.[22] This report may be affected by sampling error of Takayasu arteritis data with long-standing and complicated disease with mixed causes of PH, lead to a biased estimation of true incidence. Kalfa et al. had reported a low incidence of PH after the exclusion of Takayasu arteritis with PH secondary to left heart disease.[23] However, in the current study, echocardiographic evaluations confirmed that none of our PH patients primarily developed PH secondary to LHD, due to a valvular affection or an ischemic heart disease.

Echocardiography

The tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/sPAP) ratio is the echocardiographic estimate of RV/PA coupling measured invasively by RHC.[24] In a study by Grimaldi et al. on systemic sclerosis patients, TAPSE/sPAP ratios were lower in SSc compared to healthy control (SSc median = 0.71 vs. HC median = 1.00; $p < 0.001$) which was independently associated with RV dysfunction.[25] Moreover, TAPSE/sPAP was shown to be a more sensitive parameter associated with functional class and exercise capacity.[26,27] In the same manner, in our study, TAPSE/sPAP ratios differ especially between Group 1 and 2 Function class (1.2 ± 0.16 vs 0.83 ± 0.24, $p = 0.018$) which did not meet the PH criteria. Based on the echocardiographic studies, it was suggested that right ventricular diastolic dysfunction could be detected even in the presence of normal sPAP, probably due to vasculitis per se and to the associated pulmonary vasculopathy.[25]

Functional class and symptoms in TA

In the current study, six patients (20%) complained of respiratory symptoms, ten were also had impaired functional class (II and III), six of them had FC II and no evidence of PH in echocardiography. In this study, distance covered in 6MWT declined in proportion to the grading of NYHA functional class (FC) (Table 3). Dos Santos et al. reported in a study using IPAQ-SF (International Physical Activity Questionnaire—Short form) lower aerobic and walking capacity in TAs compared to healthy controls ($P < 0.05$).[28] This implicate that 6MWT could be interpreted not only as an indirect assesment of cardiopulomoary heomdynamic, but also as an index of patient disability.

As evident in Table 2, the overall incidence of respiratory symptoms in TAs in literature is 16.5% which is comparable to the incidence of PAI (19.3%). This also poses a screening challenge; whether TA without respiratory symptom, should be assessed regularly via transthoracic echocardiography and/or imaging or according to the emergence of pulmonary symptoms.[29]

It was hypothesized that chronic course of stenosis causes a development of bronchial-pulmonary arteries communication and recanalization, namely a "*vessel in vessel*" phenomena.[30] This may explain the higher threshold of developing symptoms and near-normal preservation of pulmonary function despite extensive arterial involvement in some cases.[15,30] However, as lesions progress, compensatory mechanisms may become overwhelmed and complicating the course of disease. The PH induced by pulmonary arteritis has shown to be correlated with extent of vascular obstruction and subsequent ischemia.[16,17] However, observations in Takayasu arteritis-associated pulmonary hypertension, especially the vasodilators-responsive patients, suggest that neurohumoral activation and endothelial dysfunction (e.g., endothelin-1) may also play a role.[31]

Age and onset of PAI

Recent studies have reported that Takayasu arteritis cases with longer disease duration are at higher risk of pulmonary artery involvement development[32] and mortality due to PAI-associated sequels.[17] Additionally, it has been shown that PAI-associated PH has a significantly longer disease duration compared to those without PH (24 vs. 6 months, $p = 0.05$),[2] implicating the insidious nature of vascular damage leading to PH. However, in our study, we did not find a difference between PH and non-PH groups regarding age and disease duration, which might be due to the small sample size of the study. On the other hand, in an American cohort among 92 Takayasu arteritis patients, more than one-third of patients developed cardiopulmonary involvements only within six months of initial presentation. This emphasizes that age and disease duration are unreliable indicators for initiation of pulmonary involvements evaluation and searching for occult PAI and PH should be warranted even at younger ages.[1]

ESR and PAI

In this study, no significant difference was noted in ESR level between PH and non-PH groups. This is in contradiction to the findings of a Korean series in which clinically active patients had a higher percentage of PAI (18.1% vs. 3.3%) and PH (44% vs. 11.1%).[33] However, a higher proportion of LHD in the active group makes the interpretation difficult, whether elevated ESR is directly related to the inflammatory process of pulmonary arteritis or not. Consistent with our results, most series in recent years could not find such an association between ESR level in TA cases with and without PH.[1,2,18,34] Surprisingly, in recent reports, ESR elevation was reported to even less frequent in patients with PH (22.9 ± 21.1 vs. 11.1 ± 14.8, $p = 0.009$).[18,35] It is speculated that in the PH subgroups with a normal level of inflammatory markers, the disease flare in pulmonary arteries is completed and more severe vascular narrowing could be expected.[3]

PFT and PAI

This study is among the first studies evaluating pulmonary function tests in patients with Takayasu arteritis. Generally, PH patients show mild restrictive patterns, which in our TA-PH patients were reflected in mild decreased DLCO (62% of predicted, $p = 0.003$). Some factors contribute to decline of DLCO such as an increase in pulmonary vascular resistance, reduced cardiac output, and local micro-thrombosis, and reduced pulmonary capillary blood volume (Dc).[36]

Lower $FEV_1\%$ (69.5 ± 6.8 vs. 87.5 ± 12.8; $p = 0.015$) can be explained by deconditioning due to weak functional status in our PH patients. Furthermore, it was hypothesized that in pulmonary hypertension, persistent obstructive-dysfunctional endothelial vicious cycle in pulmonary arteries may result in distal small vessel pulmonary vasculopathy, as seen previously in chronic thromboembolic pulmonary hypertension.[37] Moreover, it was shown that level of endothelin-1 (ET1) is increased in PH patients and are correlated with sPAP, particularly in those with Takayasu-related PH ($r = 0.33$, $p = 0.04$).[31] The activation of the ET-1 cascades as a potent vasoconstrictor and bronchoconstrictor could induce vascular remodeling, as well as small airway reactivity and contribute to airway reaction.[38] On the other side, as demonstrated by Umehara et al., Takayasu arteritis cases with extensive perfusion defects may have only slightly decreased $FEV_1\%$ compared to cases with normal scan ($p = 0.14$). This is probably due to the larger lung physiologic reserve and compensatory mechanisms. However, the researchers did not mention PH status of the patients.[15] Further studies are

needed to clarify the interaction of ET-1 system and small airways changes in TA-related PH.

Limitations

This study had some limitations. First, due to the rare nature of the disease, the sample size was relatively small. Also, the diagnosis of PH was mainly dependent upon echocardiography and we were not able to perform RHC as the gold standard to confirm all PH diagnosis.

Conclusions

The incidence of PH in Takayasu arteritis was not uncommon complication, and comparable to incidence of respiratory symptom. Therefore, it seems reasonable to lower the screening threshold preferably initiated at younger ages or in new onset patients or in Takayasu patients with pulmonary symptoms and altered functional capacity. TAPSE/sPAP could be used for early PH probability risk stratification in TAs in association with functional capacity. However, further studies are needed to determine prognositic value of TAPSE/sPAP in Takayasu vasculitits.

Ethical consideration

The protocol for the research and data collection was approved by the Institutional Ethics Committee (Approval ID: IR.TBZMED.REC.1397.388).

Conflict of interest

Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.reumae.2025.501994.

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