

Sarkoidozlu Hastalarda Sistolik Pulmoner Arter Basıncının Pulmoner Arter Çapı, Yaş, Hastalık Süresi, Hastalığın Evresi ve Akciğer Dışı Tutulumla İlişkisi

The Association of Systolic Pulmonary Artery Pressure with Pulmonary Artery Diameter, Age, Disease Duration, Stage of the Disease, and Extrapulmonary Involvement in Patients with Sarcoidosis

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ÖZ

Amaç: Sarkoidozlu hastalarda sistolik pulmoner arter basıncının (sPAB) pulmoner arter çapı (PAÇ), yaş, cinsiyet, hastalık süresi, hastalığın evresi, akciğer dışı tutulum ve spontan remisyon ile olan ilişkilerini araştırmayı amaçladık.

Materyal ve Metot: Çalışmaya göğüs hastalıkları kliniğinde 2010-2020 yılları arasında tanı almış ve takip edilmiş 60 sarkoidozlu hasta alındı. Hastaların demografik verileri, klinik seyri, tedavi bilgileri radyolojik ve ekokardiyografik incelemeleri kaydedildi. EKO'ya dayalı ortalama PAB'nın hesaplanmasında sPAB kullanıldı. PAÇ toraks BT konusunda yetkin radyolog tarafından ölçüldü. PAB ile PAÇ ve diğer parametreler arasındaki ilişki araştırıldı.

Bulgular: Hastaların sPAB: 29,68±5,73 mmHg, PAÇ: 28,20±5,75 mm olarak bulundu. Aralarında anlamlı korelasyon saptandı ($r=0,46$ $p<0,001$). PAÇ, PH'u olan hastalarda: 39,7±4,6, olmayanlarda: 27±4,9 ($p<0,001$) idi. sPAB, ekstrapulmoner tutulumu olmayanlarda: 31,03±6,35, olanlarda: 27,52±3,77 ($p=0,01$) bulundu. Araştırılan diğer parametrelerle anlamlı ilişki saptanmadı.

Sonuç: Sarkoidozlu hastalarda sPAB ve PAÇ arasında orta derecede kuvvetli pozitif yönlü korelasyon saptandı. Aynı zamanda PAÇ, PH olan hastalarda olmayanlara göre anlamlı olarak daha yüksek bulundu. Bu da sarkoidozlu hastalarda toraks BT incelemesi esnasında kolaylıkla ölçülebilen PAÇ'nın sarkoidozla ilişkili pulmoner hipertansiyonu (SIPH) tahmin etmede yol gösterici olabileceğini göstermektedir.

Anahtar Kelimeler: Pulmoner arter çapı, pulmoner hipertansiyon, sarkoidoz, sistolik pulmoner arter basıncı

ABSTRACT

Objective: We aimed to investigate the association of systolic pulmonary artery pressure (sPAP), with pulmonary artery diameter (PAD), age, gender, disease duration, disease stages, extrapulmonary involvement, and spontaneous remission in patients with sarcoidosis.

Materials and Methods: Diagnosed and followed-up in the chest diseases clinic between 2010-2020, 60 sarcoidosis patients were included. Patients' demographic data, clinical course, information over treatment, radiological and echocardiographic examinations were recorded. sPAB was utilized to calculate mean PAP based on ECHO. PAD was measured by an experienced radiologist in thoracic CT. Associations of PAP and PAD with other parameters were investigated.

Results: sPAP and PAD were found as 29.68±5.73 mmHg and 28.20±5.75 mm. A significant correlation was detected between them ($r=0.46$ $p<0.001$). PADs were 39.7±4.6 and 27±4.9 in patients with and without PH ($p<0.001$). sPAPs were found as 27.52±3.77 and 31.03±6.35 among those with and without extrapulmonary involvement ($p=0.01$). No association was found between these parameters and others.

Conclusion: A moderately strong positive correlation was detected between sPAP and PAD in sarcoidosis patients. PAD was significantly found higher in patients with PH than those without. This also shows that PAD, which can be easily measured during thoracic CT examination in sarcoidosis patients, can be a guide in predicting sarcoidosis-associated pulmonary hypertension (SAPH).

Keywords: Pulmonary hypertension, pulmonary artery diameter, sarcoidosis, systolic pulmonary artery pressure

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INTRODUCTION

As an inflammatory disease of unknown cause, sarcoidosis is characterized by the formation of granulomas in the affected organs, mostly in the lungs. The disease develops in genetically susceptible individuals through the exposure to an unknown antigen as yet.¹ Pulmonary hypertension (PH), defined as the mean pulmonary artery pressure (PAP) of ≥ 25 mmHg² by right heart catheterization (RHC), is a well-known complication of sarcoidosis and associated with a significant increase in mortality.³ However, echocardiography (ECHO) is used as an important device in the assessment of sarcoidosis-related pulmonary hypertension (SAPH).⁴ Pulmonary hypertension (PH) is a fearful complication in patients with sarcoidosis since it is an important negative prognostic factor for lung transplantation to be required in these patients at an advanced stage.⁵ PH is considered to be a vasculopathy caused by the excessive growth of vascular cells along with inflammation playing a major role in the process.⁶ SAPH is witnessed in 5 to 20% of sarcoidosis patients. Increased PAP may be due to comorbidities such as cardiac sarcoidosis and sleep apnea, as well as many factors such as vasculocentric, parenchymal, and mechanical effects. Fibrotic lung disease is encountered in most patients with SAPH; however, SAPH may also be seen in those without advanced parenchymal lung disease. In sarcoidosis, while PH is often associated with pulmonary fibrosis, a recent multinational study has reported that almost 25% of PH cases associated with sarcoidosis were radiological stages 2 and 3,⁷ suggesting that PH is of a multifactorial mechanism. In two recent studies conducted in two major reference centers and investigating the predictors of mortality in pulmonary sarcoidosis, high-resolution computerized tomography (HRCT) showed that more than 20% of pulmonary fibrosis and PH are independent predictive factors of mortality.^{8,9} In another international study performed with the same purpose, systolic pulmonary artery pressure (sPAP), carbon monoxide diffusing capacity (CMDC), and 6-minute walking distance (6MWD) were demonstrated to be statistically significant predictors of transplant-free survival in patients with SAPH.⁷

In our study, we aimed to investigate the association between sPAP, so important for sarcoidosis patients, and pulmonary artery diameter (PAD), age, disease duration, stages of the disease, and extrapulmonary involvement.

MATERIALS AND METHODS

The present study was performed by following under the Declaration of Helsinki Good Clinical Practice Guidelines in 1964 and later amendments and approved by the Ethics Committee of the Medical Faculty of Necmettin Erbakan University (Date: 04/12/2020, decision no: 2020/2930). In the study, 110 sarcoidosis patients were diagnosed and followed-up clinically, radiologically, and histopathologically in the department of chest diseases between 2010 and 2020. The data related to all sarcoidosis patients over 18 years of age were obtained by scanning the patients' files and from the hospital information management system. Thirty-two patients due to exclusion criteria and 18 patients due to missing follow-up data were excluded from the study. Therefore, 60 patients with sarcoidosis completed the study. The patients with any metabolic disease, any type of cancers, rheumatological disease, vasculitis, inflammatory bowel disease, hematological disease, autoimmune disease, and those with cardiovascular disease or other pulmonary diseases other than the cardiac involvement of sarcoidosis were not included in the study.

In the study, sarcoidosis was diagnosed by demonstrating the epithelioid cell granulomas histopathologically without caseous necrosis in biopsies taken by the endobronchial ultrasound-guided transbronchial needle aspiration biopsy (EBUS-TBNA) and mediastinoscopic methods in the company with clinical and radiological findings, and by ruling out other causes of granulomatous inflammation.¹⁰

The features such as patients' age and gender, results of thoracic computerized tomography (CT) and HRCT, stages sarcoidosis at the time of diagnosis, results of ECHO, the data, and findings after consultations about extrapulmonary involvement, the treatment modalities, and the history of patients' clinical course and epicrisis reports were recorded. Sarcoidosis patients were staged as follows: Those with normal chest radiology as stage-0, those with hilar LAPs as stage-1, those with parenchymal involvement, and hilar LAPs as stage-2, those with only parenchymal involvement as stage-3, and those with pulmonary fibrosis as stage-4.¹¹ The method used to diagnose PH definitely is RHC.⁴ However, we used the systolic PAP (sPAP) as the basis to calculate the mean PAP based on ECHO (mean PAP=0.61xsPAP+2 mmHg),¹² since our study was

retrospectively designed and the patients' RHC measurements were not performed. While the mean PAP was accepted as ≥ 25 mmHg PH, PAD was also measured at the bifurcation level along the line from the center of the adjacent ascending aorta perpendicular to the axis of the main pulmonary artery by a radiologist with expertise in thoracic CT.¹³ The measurements of PAD were performed through thoracic CT taken simultaneously with ECHO. In our study, the associations between sPAP, and PAD, age, gender, disease duration, stages of the disease, extrapulmonary involvement, and spontaneous remission were investigated.

Statistical analysis: Statistical analyses of the study findings were evaluated with the Statistical Package for the Social Sciences software, version 24.0 (SPSS Inc., Chicago, IL, USA). The analyses were performed for the appropriateness of normal distribution. In terms of the correlations, while the variables with normal distribution were assessed with the Pearson correlation test, those with no normal distribution were measured using the Spearman correlation test. The student T-test was used for the inter-group comparisons. The Mann-Whitney U test was used for two-group comparisons without normal distributions. The Kruskal Wallis test was performed for the variables in multi-group comparisons, In all analyzes, a p-value of <0.05 was accepted to be significant.

RESULTS

The patients' average age was found as 56.45 ± 14.75 years. Of 60 sarcoidosis patients, 46 were female, and 14 were male (Table 1). While the mean sPAP values of our patients were found to be 29.68 ± 5.73 mmHg (min-max: 22 and 45), the mean PAD was also detected as 28.20 ± 5.75 mm (min-max: 19 and 46) (Table 2).

A moderately powerful positive correlation was found between sPAP and PAD ($r=0.46$, $p<0.001$). There were seven (11.7%) PH patients with a mean PAP of ≥ 25 mmHg. PAD was found to be statistically significantly higher in patients with PH ($p<0.001$) (Table 3).

The mean sPAP of female patients was determined as 30 ± 6.24 mmHg, while male patients' mean sPAP was 28.64 ± 3.62 mmHg ($p = 0.44$), and there was no statistically significant difference between both genders' sPAP values.

The mean PAD in female patients was 28 ± 5.46 mm, and the mean PAD among male patients was detected as 28.86 ± 6.79 ($p=0.62$). There was no

statistically significant difference between the PAD values of both genders.

In our study, it was also investigated whether there was a correlation between the patients' age, and sPAP and PAD; however, no significant correlation was found [for PAP ($r=0.15$, $p=0.22$) and PAD ($r=0.21$, $p=0.09$)].

Although there was no extrapulmonary involvement in 37 (61.7%) of our patients, various involvements were determined in 23 patients as follows: Skin in seven patients at most, cardiac in six, Löfgren syndrome in five, Heerfordt syndrome in two, eye in one, kidney in one, and rectum in one patient (Table 1).

The values of sPAP were seen to be significantly higher in patients without extrapulmonary involvement than those with extrapulmonary involvement (31.03 ± 6.35 and 27.52 ± 3.77 , $p=0.01$). None of seven patients determined to have PH had extrapulmonary involvement. Compared the patients with and without extrapulmonary involvements in terms of PAD, the values were slightly higher in those without extrapulmonary involvement (28.81 ± 5.4 and 27.22 ± 6.15); however, the difference was not statistically significant.

The mean disease duration of our sarcoidosis patients was found as 4.06 ± 2.79 , and it was investigated whether there was a correlation between disease duration, and sPAP and PAD. Even so, no significant correlation was found [for sPAP ($r=-0.007$, $p=0.95$) and for PAD ($r=0.06$, $p=0.6$)].

When the values of sPAP and PAD were compared in terms of the stages of the disease, no significant difference was found between sPAP and PAD values ($p=0.25$ for sPAP and $p=0.28$ for PAD).

Compared sarcoidosis patients with and without spontaneous remission, no significant difference was found between those with and without spontaneous remission (for sPAP $p=0.25$ and PAD $p=0.55$).

Of our 60 patients, 28 (46.6%) were determined to be administered with the systemic steroid therapy due to the indications. While two patients were treated with the combination of methotrexate and prednisolone, two patients and one patient were detected to receive the treatments with non-steroidal anti-inflammatory drugs (NSAIDs) and infliximab, respectively (Table 1). Given the measurements of one stage-4 patient (sPAP, 45-55 mmHg before and after treatment) and three stage-2 patients (sPAP values, 43-47, 45-37, and 40-35 mmHg before and after treatment) among those with PH, no significant difference was determined.

However, when the patients receiving systemic steroid treatment (methylprednisolone) were compared with those who did not, sPAB values were measured as 28.5 ± 5.58 mmHg among those receiving systemic steroid treatment and 30.59 ± 5.69 mmHg in those not receiving the treatment, and there was no significant difference between these two groups. No significant difference was also found between those receiving systemic steroids and those who did not in terms of PAD values (27.96 ± 6.3 in those receiving the treatment, and 28.88 ± 5.37 in those who did not)

DISCUSSION AND CONCLUSION

In our study, a moderately powerful positive significant correlation was determined between sPAP and PAD. The values of PAD was also found to be statistically significantly higher among the patients with PH. These findings suggest that PAD, which can be easily measured in examining thoracic CT in sarcoidosis patients, can be a guide in predicting SAPH.

In the study where PAD was similarly investigated to predict PH in pulmonary sarcoidosis, Huitema et al. also suggested that the diameter of PA indexed to the body surface area (BSA) is a reliable predictor of PH in the patients with pulmonary sarcoidosis, and thus reported that the measurement of PA on thoracic CT may be valuable in pulmonary sarcoidosis.¹⁴

In our study, sPAP was found to be significantly higher in those without extrapulmonary involvement (31.03 ± 6.35 and 27.52 ± 3.77 , $p=0.01$). Considering the patients with extrapulmonary involvement, however, the fact that sPAP was found to be significantly lower suggests that PH, which is a predictor of poor prognosis in the condition, is less commonly seen in this disease, and this can also be used to predict the good prognosis.

Although the first case of PH in sarcoidosis was described in 1949,¹⁵ its exact prevalence remains unclear. Three previous studies of great importance in the field reported that the prevalences of PH were 5,7%, 14%, and 20.8%.¹⁶⁻¹⁸ In these studies, the right ventricular systolic pressure (RVSP) was based to be ≥ 40 mmHg on the diagnosis of PH (if there is no significant stenosis in the right ventricular orifice or pulmonary valve, RVSP is equivalent to sPAP). Similarly, the prevalence of PH was also found to be 11.7% in our patients. In the current Pulmonary Hypertension in Sarcoidosis (PULSAR) study, the prevalence of PH was found as 3% in predominantly

Caucasian-originated individuals consisting of 400 sarcoidosis patients using ECHO, and if indicated RCC, and it was reported in the study that ethnic differences may play a role in the prevalence of PH.¹⁹

In a previous important study, PH was suggested to be associated with the prevalence of stage-4 parenchymal disease.²⁰ In this study, while 60% of those with PH were seen to be stage-4 patients, another stage was not observed as prominent among those without pulmonary HT. In the study investigating the same entity and performed by Shlobin et al. as one of the latest multinational studies, it has been reported that 65.6% of the patients with PH had stage-4 diseases, and only 2% were stage-1 patients.⁷ Of seven patients with SAPH in our study, four were stage-2 patients, two were stage-1, and only one patient was at stage-4. Even so, when all patients were compared in terms of sPAP and PAD according to the stages, no significant difference was found between both groups.

Although a response rate between 20-30% has been reported in small series treated with anti-inflammatory drugs in SAPH, the treatment with anti-inflammatory drugs has shown no consistent benefit²¹. In neither the International Registry for Sarcoidosis Associated Pulmonary Hypertension (ReSAPH)⁷ nor the large-scale French study³, the steroid treatment was not associated with better results. In our study, no significant difference was found between the measurements of sPAP before and after the treatment in our patients with PH. Besides, whether there was a significant difference was also investigated in sarcoidosis patients with and without spontaneous remission in terms of sPAP and PAD. Compared sarcoidosis patients with and without spontaneous remission, no significant difference was found between those with and without spontaneous remission.

In our study, no significant difference was found between the female and male patients in terms of sPAP and PAD. Additionally, there was no significant correlation between the patients' age and disease duration, and sPAP and PAD.

Limitations of the study: Our study has also some limitations. One of the important limitations is that PH could not be demonstrated by RHC. Besides, our study was performed in a single-center, and the number of our study participants is limited. So, we consider our findings cannot be generalized.

In conclusion, there is a moderately powerful posi-

tive correlation between sPAP and PAD in the patients with sarcoidosis, and PAD was also found to be significantly higher in the patients with PH than those without. This also reveals that PAD, which can be easily measured during the examination of thoracic CT in sarcoidosis patients, can be used as a guide in predicting SAPH. For this reason, we consider that more comprehensive prospective studies including RHC are needed to elucidate the relationship of PAD and PAP.

Ethics Committee Approval: The study was approved by the Ethics Committee of the Medical Faculty of Necmettin Erbakan University (Date: 04/12/2020, decision no: 2020/2930).

Conflict of Interest: No conflict of interest was declared by the authors.

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Table 1. Demographic and clinical characteristics.

Age	56.45±14.75		
		N	%
Gender	Female	46	77
	Male	14	23
The stages of the disease	Stage 1	21	35
	Stage 2	34	57
	Stage 3	4	6
	Stage 4	1	2
Extrapulmonary Involvement	No	37	61.7
	Skin	7	11.7
	Heart	6	10.0
	Löfgren syndrome	5	8.3
	Heerfordt syndrome	2	3.4
	Eyes	1	1.7
	Kidneys	1	1.7
	Rectum	1	1.7
Medications used for treatment	No (follow-up without medications)	29	48.3
	Methylprednisolone	26	43.3
	Methylprednisolone+methotrexate	2	3.3
	NSAIDs	2	3.3
	Infliximab	1	1.7

N: Number of patients, NSAIDs: Non-steroidal anti-inflammatory drugs.

Table 2. Association between systolic pulmonary artery pressure and pulmonary artery diameter.

	N	Mean±SD	Min-Max	r	p
sPAP (mmHg)	60	29.68±5.73	22-45	0.46	<0.001
PAD (mm)	60	28.20±5.75	19-46		

Min-Max: Minimum and maximum values; N: Number of patients; PAD: Pulmonary artery diameter; SD: Standard deviation; sPAP: Systolic pulmonary artery pressure; r: Correlation coefficient.

Table 3. Comparison of PAD between both groups with and without PH.

	PAP Mean±SD	PAD Mean±SD	PAP Median (Min- Max)	PAD Median (Min- Max)	*p
Patients with PH (n=7)	27.3 ±1.9	39.7 ±4.6	28 (25-29)	38 (28-41)	<0.001
Patients without PH (n=53)	19 ±2.9	27 ±4.9	19 (15-29)	26 (19-46)	

Min-Max: Minimum and maximum values; PAD: Pulmonary artery diameter,; PAP: Pulmonary artery pressure; PH: Pulmonary hypertension; SD: Standard deviation; *A p value is $p < 0.001$ for mean and median values.