Incidence of Pulmonary Hypertension and Its Clinical Relevance in Patients With Sarcoidosis*

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Objective: **To investigate the frequency of pulmonary hypertension (PH) and clinical parameters associated with PH in sarcoidosis patients.**

Methods: **A prospective, observational study was performed on 246 consecutive Japanese sarcoidosis patients followed up at the outpatient sarcoidosis clinic in the Central Clinic of Kyoto. The patients were evaluated for PH by Doppler echocardiography. Among these patients, 192 underwent pulmonary function tests. In addition, high-resolution CT of the lung was evaluated for the presence of lymph node enlargement, lung opacity, and thickening of bronchovascular bundles in 122 patients. PH was defined as estimated systolic pulmonary artery pressure (sPAP) ≥ 40 mm Hg. The frequency of PH was evaluated, and clinical parameters were compared between patients with PH and those without PH.**

Results: **Among 212 patients who were successfully evaluated for sPAP, 12 patients (5.7%) had PH. Patients with PH had the following clinical characteristics: advanced chest radiographic stage, decreased oxygen saturation, predominantly male gender, and decreased percentage of predicted vital capacity, percentage of predicted FVC, percentage of predicted FEV_1, percentage of predicted functional residual capacity, and percentage of predicted total lung capacity (%TLC). Multivariate logistic regression analysis showed that decreased %TLC was independently associated with PH. There was a weak negative correlation between sPAP and %TLC ($p < 0.05$).**

Conclusions: **The frequency of PH in Japanese sarcoidosis patients was 5.7% evaluated with Doppler echocardiography. Decreased lung volume increases the risk of PH developing in patients with sarcoidosis.** ***(CHEST 2006; 129:1246–1252)***

Key words: CT; epidemiology; pulmonary function test; pulmonary hypertension; sarcoidosis

Abbreviations: BHL = bilateral hilar lymphadenopathy; CI = caval index; DE = Doppler echocardiography; D_{LCO} = diffusion capacity of the lung for carbon monoxide; $\%FEV_1$ = percentage of predicted FEV_1; %FRC = percentage of predicted functional residual capacity; %FVC = percentage of predicted FVC; HRCT = high-resolution CT; IVC = inferior vena cava; PAP = pulmonary artery pressure; PFT = pulmonary function test; PH = pulmonary hypertension; RAP = right atrial pressure; RHC = right-heart catheterization; sACE = serum angiotensin-converting enzyme; sPAP = systolic pulmonary artery pressure; Spo_2 = oxygen saturation; %TLC = percentage of predicted total lung capacity; TLC = total lung capacity; %VC = percentage of predicted vital capacity

Sarcoidosis is a systemic granulomatous disease of unknown cause. Any organ can be involved, and the intrathoracic lymph nodes and lungs are most commonly affected. Pulmonary hypertension (PH) is a life-threatening complication of several lung diseases, and it has been reported that the presence of PH adversely affects survival of sarcoidosis patients.[1]

The frequencies of PH in sarcoidosis patients in previous reports[2–6] varied from 1 to 28% depending on the definition of PH and entry criteria of patients. Recently, Shorr et al[7] reported that the frequency of PH was as high as 73.8% in 363 advanced sarcoidosis patients listed for orthotopic lung transplantation. Among these reports, study patients were limited to those with advanced lung diseases in one study,[7] while others[2–5] comprised small number of patients (21 to 50 cases). There have been no reports regarding the epidemiology of PH in an adequate number of sarcoidosis patients with various degrees of severity of the disease. This might be due to the difficulty

in performing invasive assessment of pulmonary artery pressure (PAP) in all sarcoidosis patients including those with minimal disease severity.

Regarding the mechanism of the development of PH in sarcoidosis, some authors[6] believe that parenchymal involvement in sarcoidosis causes fibrosis and destruction of the pulmonary vessels, resulting in an irreversibly obliterated pulmonary vascular bed. However, vascular involvement of sarcoidosis can cause PH in the absence of significant pulmonary fibrosis,[8] and extrinsic compression of pulmonary arteries by enlarged mediastinal lymph nodes can also cause PH in sarcoidosis.[9] Based on these reports, the causes of PH in sarcoidosis are considered to be variable; however, the mechanism most frequently involved in the development of PH in sarcoidosis has not been fully elucidated. According to the possible mechanisms mentioned above, we hypothesized that PH is likely to be more common in patients with advanced lung disease with impaired lung functions, or in those with enlarged lymph nodes. However, no previous study investigated the relationship between lymph node enlargement and PH, and it had been reported[3] that there was no correlation between PH and lung functions.

In this study, we aimed to investigate the frequency of PH in sarcoidosis patients who were being followed up at the outpatient clinic. To investigate the presence of PH in a large number of patients, Doppler echocardiography (DE) was selected as a screening method to estimate systolic PAP (sPAP). Next, we investigated the correlation between the presence of PH and several clinical parameters, including lung function tests and lymph node enlargement detected on chest CT.

Materials and Methods

Study Population

The study population comprised 246 Japanese sarcoidosis patients with histologic confirmation of the diagnosis. All patients were being consecutively followed up at the outpatient sarcoidosis clinic in the Central Clinic of Kyoto during the period between August 2004 and April 2005. Patients with concurrent collagen vascular diseases or other lung diseases were excluded from the study. The following procedures were performed in the study patients. DE was used to measure sPAP, and classification of chest radiographs (stage 0, normal; stage I, bilateral hilar lymphadenopathy [BHL]; stage II, BHL with pulmonary infiltrations; stage III, pulmonary infiltrates without BHL; stage IV, pulmonary fibrosis) was performed at the same time. Combined extrapulmonary lesions[10] were also investigated. Transcutaneous oxygen saturation (Spo_2) in room air was recorded with a pulse oximeter (PULSOX-M; Teijin Pharma; Tokyo, Japan) after 10 min of rest in sitting position to achieve stable values. Serum angiotensin-converting enzyme (sACE) was measured.

Among 246 patients, 192 underwent pulmonary function tests (PFTs), and high-resolution CT (HRCT) was performed in 122 cases on the same day of DE procedure. Patients who had already undergone PFTs and/or HRCT shortly before the DE procedure did not undergo these tests again; however, these patients were not clinically different from the others. The study was approved by ethics committees in Kyoto University, and informed, written consent was obtained from all patients.

DE Technique and Measurement of sPAP

DE was performed using conventional clinical echocardiographic equipment (ProSound SSD-6500SV; Aloka; Tokyo, Japan) with transducers. Transthoracic Doppler and two-dimensional images were obtained from parasternal long and short axes and apical four-chamber views. Ejection fraction was calculated from diastolic and systolic left ventricular diameters obtained from long-axis view. Tricuspid regurgitant flow was identified by color-flow Doppler techniques, and the maximum jet velocity was measured by continuous-wave Doppler. Right ventricular systolic pressure was estimated based on the modified Bernoulli equation and was considered to be equal to the sPAP in the absence of right ventricular outflow obstruction: sPAP = right ventricular systolic pressure = transtricuspid gradient + right atrial pressure [RAP], where transtricuspid gradient is $4v^2$ (v = peak velocity of tricuspid regurgitation in meters per second).[11]

RAP was estimated by measuring the percentage of collapse of inferior vena cava (IVC) diameter during inspiration based on the technique reported by Kircher et al.[12] Briefly, IVC diameters were measured from long-axis subxiphoid views with the patient in a supine to 30° upright position. All measurements were made within 2 cm of the right atrial origin of the IVC. The minimum inspiratory and maximum expiratory diameters of the IVC were recorded. The caval index (CI) was defined as the percentage decrease in diameter of the IVC with inspiration. Based on the regression line of CI vs RAP shown by Kircher et al,[12] RAP was estimated to be as follows: CI $< 35\%$, RAP = 15 mm Hg; CI $\geq 35\%$ to $< 60\%$, RAP = 10 mm Hg; and CI $\geq 60\%$, RAP = 5 mm Hg.

PH was defined as sPAP $\geq$ 40 mm Hg. This value was chosen based on the criteria established by the World Health Organization Symposium on Primary Pulmonary Hypertension (1998), which defines mild PH as a sPAP of 40 to 50 mm Hg.

Measurement of sACE

sACE activity was measured using the method of Kasahara and Ashihara,[13] with optical density measurements at 505 nm and 800 nm with a spectrophotometer. Serum samples were considered to be positive if they contained > 21.4 IU/L.

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