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 FEV1, 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.

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

Abbreviations: BHL = bilateral hilar lymphadenopathy; CI = caval index; DE = Doppler echocardiography; DLco = diffusion capacity of the lung for carbon monoxide; %FEV1 = percentage of predicted FEV1; %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; SpO2 = 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 reports2–6 varied from 1 to 28% depending on the definition of PH and entry criteria of patients. Recently, Shorr et al7 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 others2–5 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,\(^6\) 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 infiltrates; 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 = transticuspid gradient + right atrial pressure (RAP), where transticuspid 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.
The HRCT scans (Pronto SE; Hitachi Medical; Tokyo, Japan) were obtained using 2-mm collimation, scan time of 1.0 s, 120 kilovolt peak, and 200 mA. The HRCT images were assessed for the presence of the following: (1) mediastinal and/or hilar lymph node enlargement; (2) opacities in the lung field; and (3) thickening of bronchovascular bundles. The CT scans were assessed in random order by two independent assessors (T.H. and Y.F.), and a consensus was reached by both observers.

**Lung Function Testing**

All PFTs were performed according to the American Thoracic Society guidelines.\(^{14,15}\) Vital capacity, FVC, FEV\(_1\), mean forced expiratory flow during the middle half of the FVC, maximum expiratory flow at the quartile of FVC, functional residual capacity, total lung capacity (TLC), residual volume, and the diffusion capacity of carbon monoxide (DLCO) were measured (Chestac-8800; Chest M.I.; Tokyo, Japan). Published equations were used to determine predicted values of each parameter.\(^{16–18}\)

**Statistical Analysis**

Statistical analyses were performed (Statview; SAS Institute; Cary, NC). All the variables noted above were compared between subjects with PH and those without PH. Comparison of categorical data were made using the \(\chi^2\) test or Fisher exact probability test. Continuous variables were compared with unpaired \(t\) test if normally distributed and Mann-Whitney \(U\) test when the distribution was not normal. In the comparison of multiple indexes of PFTs and the frequency of several extrapulmonary lesions, data were adjusted for multiple comparisons by the Bonferroni approach. Spearman rank correlation coefficient was used to analyze the correlation between two samples. Logistic regression analyses were performed to investigate the independent effect of different variables on PH; \(p < 0.05\) was considered statistically significant.

**Results**

**Frequency of PH**

Measurement of sPAP was possible by DE in 212 of 246 patients (86%). Tricuspid regurgitant flow was absent in the rest of the subjects. Among subjects with successful PAP measurement, 12 of 212 patients (5.7%) had sPAP \(\geq 40\) mm Hg, which fulfilled the definition of PH.

**Association of Clinical Characteristics With PH**

Comparison of clinical characteristics between subjects with PH and those without PH (Table 1) showed that male gender, advanced chest radiographic stage, and decreased \(\text{SpO}_2\) were associated with PH. Treatment history, usage of vasodilators, systemic hypertension, left ventricular function, and frequency of extrapulmonary lesions (data were shown only for cardiac involvements in Table 1) did not differ between the two groups.

**Association of PFTs With PH**

Among 192 patients who underwent PFTs, 165 patients were successfully assessed for sPAP. Com-

### Table 1—Comparison of Patient Characteristics and DE Data*

<table>
<thead>
<tr>
<th>Variables</th>
<th>sPAP &lt; 40 mm Hg</th>
<th>sPAP (\geq 40) mm Hg</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>200</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>57.6 ± 14.4</td>
<td>58.9 ± 13.0</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>48/152</td>
<td>7/5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Disease duration, mo</td>
<td>105 ± 86</td>
<td>109 ± 76</td>
<td>NS</td>
</tr>
<tr>
<td>Stage (I/II/III/IV), No.</td>
<td>94/49/27/5</td>
<td>2/3/1/2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Smoker/nonsmoker, No.</td>
<td>42/158</td>
<td>4/8</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>97.6 ± 1.0</td>
<td>96.7 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>sACE, IU/L</td>
<td>16.9 ± 7.5</td>
<td>18.1 ± 6.6</td>
<td>NS</td>
</tr>
<tr>
<td>Extrathoracic lesions, No.</td>
<td>1.5 ± 1.0</td>
<td>1.8 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac sarcoidosis (yes/no), No.</td>
<td>22/178</td>
<td>2/10</td>
<td>NS</td>
</tr>
<tr>
<td>Other cardiac diseases (yes/no), No.</td>
<td>7/193</td>
<td>1/11</td>
<td>NS</td>
</tr>
<tr>
<td>Immunosuppressant (yes/no), No.</td>
<td>103/97</td>
<td>6/6</td>
<td>NS</td>
</tr>
<tr>
<td>Vasodilator (yes/no), No.</td>
<td>30/170</td>
<td>2/9</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic hypertension (yes/no), No.</td>
<td>25/175</td>
<td>1/11</td>
<td>NS</td>
</tr>
<tr>
<td>sPAP, mm Hg</td>
<td>25.8 ± 7.0</td>
<td>44.7 ± 4.7</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>68.2 ± 9.1</td>
<td>66.8 ± 16.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD unless otherwise indicated. NS = not significant.
†Normal value, 8.3 to 21.4 IU/L.
‡Eye, \(n = 159\); skin, \(n = 51\); spleen, \(n = 25\); heart, \(n = 23\); superficial lymph nodes, \(n = 22\); kidney, \(n = 14\); nerve, \(n = 14\); muscle, \(n = 5\); liver, \(n = 3\); bone, \(n = 1\); and testis, \(n = 1\).
§Six cases were ischemic heart disease; the other two cases were atrial septal defect and valve dysfunction.
¶Previous or current treatment with oral corticosteroids, immunosuppressants, or inhaled corticosteroids.
¶¶Current treatment with calcium-channel blockers and/or angiotensin II receptor antagonists.
Association of HRCT Findings With PH

Among 122 subjects assessed for HRCT, sPAP was successfully measured in 105 subjects. In the comparison of three HRCT parameters assessed in this study, none showed a statistically significant difference between the two groups (Table 3).

Independent Factors Associated With PH

To determine whether pulmonary function indexes with statistical significance in univariate analyses were independently associated with PH, multivariate logistic regression analyses were performed to eliminate confounding factors. Based on the results of univariate analyses, SpO2 and gender of patients were included in the analysis as possible confounders. The analyses showed that decreased %TLC (per 10%) was independently associated with PH (p < 0.05; odds ratio, 0.69; 95% confidence interval, 0.48 to 0.99), although its average reduction in subjects with PH was mild. In the analysis, it was also shown that SpO2 and gender of patients were not independent determinants of PH. None of the other indexes of PFTs showed significant association with PH. Also, chest radiographic stage was not independently associated with PH when adjusted for SpO2 and gender of patients.

Table 2—Comparison of PFTs*

<table>
<thead>
<tr>
<th>Variables</th>
<th>sPAP &lt; 40 mm Hg</th>
<th>sPAP ≥ 40 mm Hg</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>154</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>%VC</td>
<td>109 ± 18</td>
<td>90 ± 24</td>
<td>0.0011</td>
</tr>
<tr>
<td>%FVC</td>
<td>106 ± 18</td>
<td>88 ± 24</td>
<td>0.0020</td>
</tr>
<tr>
<td>%FEV1</td>
<td>105 ± 19</td>
<td>87 ± 27</td>
<td>0.0035</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>80 ± 8</td>
<td>78 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>%FEF25-75</td>
<td>75 ± 29</td>
<td>56 ± 29</td>
<td>NS</td>
</tr>
<tr>
<td>%FRC</td>
<td>118 ± 25</td>
<td>92 ± 38</td>
<td>0.0014</td>
</tr>
<tr>
<td>%TLC</td>
<td>107 ± 17</td>
<td>89 ± 26</td>
<td>0.0007</td>
</tr>
<tr>
<td>%RV/TLC</td>
<td>113 ± 20</td>
<td>100 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>%DLco</td>
<td>86 ± 16</td>
<td>81 ± 27</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD unless otherwise indicated. Data of percentage of predicted peak expiratory flow, percentage of predicted maximum expiratory flow at 50% of FVC, percentage of predicted maximum expiratory flow at 25% of FVC, and percentage of predicted DLco/alveolar volume are not shown. An unpaired t test was used in the analysis, and the results were adjusted for multiple comparison by the Bonferroni approach; p < 0.0038 was considered statistically significant. %FEF25-75 = percentage of predicted mean forced expiratory flow during the middle half of FVC; %RV/TLC = percentage of predicted residual volume/TLC; %DLco = percentage of predicted DLco. See Table 1 for expansion of abbreviation.

Table 3—Comparison of HRCT Findings*

<table>
<thead>
<tr>
<th>Variables</th>
<th>sPAP &lt; 40</th>
<th>sPAP ≥ 40</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>96</td>
<td>9</td>
<td>NS</td>
</tr>
<tr>
<td>Lymph node enlargement</td>
<td>47/49</td>
<td>5/4</td>
<td>NS</td>
</tr>
<tr>
<td>Opacities in lung fields</td>
<td>50/46</td>
<td>7/2</td>
<td>NS</td>
</tr>
<tr>
<td>Thickening of bronchovascular bundles</td>
<td>11/85</td>
<td>1/8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as No.†Fisher exact probability test was used in the statistical analysis.

**Discussion**

The epidemiology of PH in sarcoidosis has not been fully elucidated due to the difficulty in performing invasive assessment of PAP in substantial number of patients with various degrees of disease severity. We investigated the frequency of PH in sarcoidosis patients who were followed up in the outpatient clinic. Clinical parameters associated with PH were also investigated.

In this study, DE was used to estimate sPAP. Although some studies19,20 have suggested that sPAP estimated by DE does not serve an accurate predictive model of sPAP measured by right-heart cathe-
terization (RHC), variability in hemodynamic readings has been described extensively and thus nonsimultaneous hemodynamic measurements may vary significantly.\textsuperscript{21,22} Shapiro et al\textsuperscript{23} showed that sPAP measured by both methodologies correlated much better when performed simultaneously, and concluded that DE was a good noninvasive estimator of actual pulmonary artery pressure.\textsuperscript{24} Based on these reports, DE was selected as a noninvasive screening method to detect PH in this study. Although sPAP was not measured in 14% of patients due to the lack of tricuspid regurgitant flow, their clinical parameters did not differ from those with successful measurement of PAP (data not shown).

The frequency of PH in this study was 5.7%. This frequency was comparable to that reported by Rizzato et al,\textsuperscript{5} who measured PAP by RHC in sarcoidosis patients in various stages, and showed that resting PH (mean PAP $\geq 25$) was found in 3 of 50 patients (6%). Although 109 of 212 patients (51%) had been currently or previously treated with corticosteroids or immunosuppressants, and 33 patients (16%) were receiving vasodilators, none of these treatments were aimed at the treatment of PH. However, we cannot exclude the possibility that these treatments led to the underestimation of PH in this study, although it was reported that the effect of corticosteroids on PAP were variable,\textsuperscript{4} and calcium-channel blockers had no effect on pulmonary hemodynamics\textsuperscript{25} in patients with sarcoidosis. Additionally, a substantial number of the patients in this study had long disease duration (average, 105 months), which might have led to overestimation of the frequency of PH in sarcoidosis compared with that evaluated at the first presentation. Although the patients referred to the Central Clinic of Kyoto have no specific characteristics compared with the general population of Japanese sarcoidosis patients, it should be noted that the frequency of PH evaluated in this study was that of patients with various lengths of disease duration including those with chronic phase of the disease.

Despite the recent recognition of the DE as a good screening method to detect PH, we still consider that DE cannot replace RHC to measure PAP accurately in individual patients; thus, we are planning to perform RHC in 12 subjects with estimated sPAP $\geq 40$ mm Hg.

The comparison of clinical parameters between patients with and without PH showed that patients with PH had advanced chest radiographic stage, decreased SpO$_2$, increased percentage of male gender, and decreased %VC, %FVC, %FEV$_1$, %FRC, and %TLC. Logistic regression analysis showed that decreased %TLC was independently associated with PH. Sulica et al\textsuperscript{26} reported the clinical characteristics of 54 sarcoidosis patients with PH compared with 52 patients without PH; the use of DE made it possible to assess PH in a large number of sarcoidosis patients with various disease severities. In this large cohort study,\textsuperscript{26} it was shown that patients with PH had...
lower spirometric measurements including %FVC, and that PH was associated with a higher prevalence of stage 4 sarcoidosis. Taken together, the results support the hypothesis that parenchymal involvement by sarcoidosis causes fibrosis, and may also destroy the pulmonary vessels, resulting in pulmonary hypertension in sarcoidosis patients. As shown in Figure 1, all subjects with %TLC of <60% had PH; in these three patients, pulmonary lesions with fibrosis were mainly distributed along the bronchovascular bundles (Fig 2), which further supports the hypothesis mentioned above. The clinical characteristics of the three patients are shown in Table 4. Other possible causes of reduced TLC aside from pulmonary fibrosis include increased elastic contractility of the chest wall, or decreased muscle strength of respiratory muscles; however, none of the subjects had concurrent neuromuscular diseases or any sign of muscle weakness due to involvement of muscles in the disease, or showed side effects of treatment with corticosteroids.

Some patients with PH, however, had normal values of %TLC (Fig 1), suggesting that other mechanisms may also be involved in the development of PH in sarcoidosis. In the analysis of HRCT findings, mediastinal and/or hilar lymph node enlargement did not affect the presence of PH. Although it was reported that the extrinsic compression of pulmonary arteries by enlarged mediastinal lymph nodes can cause PH, the role of enlarged lymph nodes in the development of PH was not demonstrated in this study. Thickening of bronchovascular bundles (fibrosis without thickening was excluded) were also investigated because they too can extrinsically compress pulmonary arteries, but they were not associated with PH either. The lack of association of HRCT parameters with PH might be due to the small number of cases evaluated for HRCT findings (only nine cases for positive PH), or alternatively, the lack of the evaluation of the size or the extent of each finding. Further studies are needed regarding the association of HRCT findings with PH in sarcoidosis.

Patients with concurrent collagen vascular diseases were excluded from the study; thus, this condition could not have contributed to the development of PH. Another possible mechanism is vascular involvement of sarcoidosis in the absence of significant pulmonary fibrosis, which might be involved in the development of PH in patients without a decrease in lung volume.

In patients with %FVC of <50%, <70%, and <60%, PH occurred in 3 of 18 patients (17%), 3 of 10 patients (30%), and 3 of 3 patients (100%), respectively. Based on the increasing frequency of PH as %FVC decreases, it seems reasonable that the frequency of PH reported by Shorr et al was much higher (73.8%), as they evaluated PH in sarcoidosis patients with advanced lung diseases whose average %FVC was <50%. In contrast, average %FVC was 105% in this study, and none of the patients were receiving supplemental oxygen. In Japan, lung diseases because of sarcoidosis are relatively mild, and the most frequent cause of death from sarcoidosis is myocardial involvement. Elsewhere, the most common cause of mortality is respiratory failure. Based on the result of this study, the frequency of PH evaluated in this study might be specific to Japanese sarcoidosis patients, and the incidence of PH in sarcoidosis might be higher in other ethnic groups with more advanced lung diseases. In fact, the frequency of PH was much higher (51%) in the study of Sulica et al, in which the majority of the subjects were black and the average %FVC was as low as 60%.

In conclusion, the frequency of PH in Japanese sarcoidosis patients who were followed up in the outpatient clinic was 5.7%. Decreased lung volume increases the risk of PH developing in patients with sarcoidosis.

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References


