Incidence and Clinical Characteristics of Chronic Pulmonary Thromboembolism in Japan Compared With Acute Pulmonary Thromboembolism — Results of a Multicenter Registry of the Japanese Society of Pulmonary Embolism Research —

Mashio Nakamura, MD; Osamu Okada, MD*; Masahito Sakuma, MD**; Norifumi Nakanishi, MD†; Yoshiyuki Miyahara, MD‡; Norikazu Yamada, MD; Hirofumi Fujioka, MD; Takayuki Kuriyama, MD*; Takeyoshi Kunieda, MD‡; Tsuneaki Sugimoto, MD‡‡; Takeshi Nakano, MD

The incidence of acute pulmonary thromboembolism (APTE) in Japan is quoted as being extremely low compared with the United States, and the incidence and clinical characteristics of chronic pulmonary thromboembolism (CPTE) in Japan is unknown, so this study investigated these aspects of CPTE in 309 patients with APTE and 68 patients with CPTE. The ratio of the incidence of CPTE to APTE was 0.22 and there was no significant difference in age or sex between the APTE and CPTE patients. All of the predisposing factors for pulmonary thromboembolism, except for thrombophilia, were more frequently seen in the patients with APTE. There are some differences in the incidence and clinical characteristics of CPTE compared with APTE between Japanese and American patients in Japan, suggesting that the pathogenesis of CPTE in Japan may differ from that in the USA. (Circ J 2002; 66: 257–260)

Key Words: Japan; Pulmonary thromboembolism; United States of America (USA)
persisted for 6 months (CPTE Group); and (3) PTE that was neither APTE nor CPTE. The diagnosis of CPTE in our registry was from right-heart catheterization and pulmonary angiography as the principal requirement. Patients with a strong clinical suspicion of CPTE but without results from right-heart catheterization or pulmonary angiography were included in the present study if they had persistently increased right ventricular afterload observed on ECG (eg, S waves in lead I combined with Q waves in lead III or negative T waves in the precordial leads V1–3)17 and echocardiography (eg, right ventricular dilatation or hypertrophy, paradoxical septal wall motion, or tricuspid regurgitation jet >2.5 m/s). All decisions concerning the diagnostic workup were made by the clinicians caring for each the patient.

Data Collection

Complete information on the clinical course of the enrolled patients was obtained from a standardized questionnaire sent to the participating clinical centers from the steering committee. Clinical symptoms and signs of the patients at diagnosis, presence of underlying diseases or predisposing factors for venous thromboembolism, diagnostic procedures and presence of deep venous thrombosis were recorded.

Statistical Analysis

Statistical analysis was performed on the incidence and clinical characteristics of APTE/CPTE in the APTE and CPTE groups only. All continuous variables were reported as mean ± standard deviation. Comparisons of proportion were made using chi-square test, or Fisher’s exact test when appropriate. Difference in the mean age between the APTE and CPTE groups was examined using an unpaired Student’s t test. All significance tests were 2-tailed, with p<0.05 considered to show statistical significance.

Results

Based on the clinical course, 309 patients (187 women, 122 men) were classified into the APTE group, and 68 (46 women, 22 men) into the CPTE group. The ratio of the incidence of CPTE to APTE during the study period was 0.22 (the incidence of APTE and CPTE by age is shown in Fig 1). The mean age at diagnosis was 62±16 years (range, 17–92 years) in the CPTE group and 60±15 years (range, 15–87 years) in the APTE group. The female/male ratio in the CPTE group was 2.1 and 1.5 in the APTE group. There was no significant difference in age or sex between the 2 groups.

Table 1 Diagnostic Workup in the Patients (n=68) With Chronic Pulmonary Thromboembolism

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary angiography with right-heart catheterization</td>
<td>40 (59)</td>
</tr>
<tr>
<td>Lung scintigraphy with echocardiography</td>
<td>27 (40)</td>
</tr>
<tr>
<td>Autopsy</td>
<td>1 ( 1)</td>
</tr>
</tbody>
</table>

Table 2 Clinical Characteristics at Diagnosis in the Patients With Acute and Chronic Pulmonary Thromboembolism (APTE and CPTE Groups)

<table>
<thead>
<tr>
<th></th>
<th>APTE group (n=309)</th>
<th>CPTE group (n=68)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>137 (44)</td>
<td>35 (51)</td>
<td>0.60</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>187/122 (1.5/1)</td>
<td>46/22 (2.1/1)</td>
<td>0.34</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>205 (66)</td>
<td>53 (78)</td>
<td>0.43</td>
</tr>
<tr>
<td>Chest pain</td>
<td>141 (46)</td>
<td>17 (25)</td>
<td>0.036</td>
</tr>
<tr>
<td>Palpitation</td>
<td>59 (19)</td>
<td>24 (35)</td>
<td>0.025</td>
</tr>
<tr>
<td>Recent major operation</td>
<td>110 (36)</td>
<td>2 ( 3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recent major trauma or fracture</td>
<td>29 ( 9)</td>
<td>0</td>
<td>0.077</td>
</tr>
<tr>
<td>Cancer</td>
<td>70 (23)</td>
<td>3 ( 4)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Prolonged immobilization</td>
<td>71 (23)</td>
<td>2 ( 3)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>99 (32)</td>
<td>26 (38)</td>
<td>0.58</td>
</tr>
<tr>
<td>Obesity (BMI ≥25.3)</td>
<td>106 (34)</td>
<td>12 (18)</td>
<td>0.060</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>17 ( 6)</td>
<td>13 (19)</td>
<td>0.0020</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>AT III deficiency</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Data presented are number (%) of patients. AT, antithrombin; BMI, body mass index.
than in the CPTE group. On the other hand, thrombophilia was more frequently seen in the CPTE group (8 patients with lupus anticoagulant, 2 with protein C deficiency and 1 with antithrombin III deficiency). These predisposing factors, other than thrombophilia, were only seen in isolated cases of CPTE; there was no significant difference between the APTE and CPTE groups in the history of deep venous thrombosis (32% vs 38%).

Discussion

In a minority of survivors of embolism, the embolic event, which is commonly not diagnosed during its acute phase, will result in organized and recanalized residua. If the obstruction is of sufficient magnitude to substantially increase right ventricular afterload, CPTE will ensue. The failure of normal embolic resolution remains one of the most intriguing questions in the pathogenesis of CPTE. The only identified thrombotic predisposition is reported to be the presence of lupus anticoagulant; approximately 10% in one report and 12% in the present study. Less than 1% of patients have deficiencies of antithrombin III, protein C or protein S! Given the annual incidence of PTE in the United States, it is likely that only 0.1–0.5% of patients suffering an acute embolic event (i.e., 500–2,500 patients per year) will develop CPTE. However, in the present study, the total number of CPTE patients was 22% of the number of APTE patients, which is a much higher percentage than seen in the United States. A similar finding has been demonstrated in a local study.

There are several reasons for this inconsistency between the US reports and ours. The first is the difference in the mechanism of CPTE development between Japanese and Western patients. There may not be a relationship between APTE and CPTE in most cases in Japan, an hypothesis that can be supported by results obtained from the present study. There was a significant difference in the predisposing factors for venous thromboembolism between the CPTE and APTE groups. The ratio of females to males in the CPTE group was higher (2.1) than that in the study conducted in the United States (ratio: 0.7) whereas the male/female ratio in the general Japanese population is 1.04. Although it had been suggested that the main cause of CPTE is deep venous thrombi that repeatedly detach and cause chronic thrombosis in the pulmonary artery, the demonstrated incidence of deep venous thrombosis associated with CPTE was not high: 38% of the present patients had deep venous thrombosis.

The second possible reason for the inconsistency could be that the frequency of diagnosing APTE correctly is extremely low in Japan. Although a recent autopsy study indicates that the incidence of APTE in Japan is comparable to that of Western countries according to a 1999 report, the clinical diagnosis of APTE in Japan is approximately 200-fold less than the rate in the United States Therefore, the actual incidence of APTE might be higher than the observed incidence. However, if the ratio of CPTE to APTE was as low as that in the United States (0.1–0.5%), APTE would have been observed in 13,600–68,000 patients in the participating clinical centers during the study period. These calculated values are not reliable.

The third possible reason was the potential inclusion of patients with pulmonary vasculitis caused by autoimmune diseases. For instance, Takayasu’s arteritis often shows defects on lung scintigraphy and pulmonary angiogram and is clinically difficult to discriminate from CPTE.

Study Limitations

We did not have definite criteria for CPTE and, in addition, we included patients with clinically suspected CPTE but without right-heart catheterization or pulmonary angiography results. Thus, our registry might include other pulmonary vessel diseases. However, because there have been few cases diagnosed with CPTE, there has not been rigorous definition and discussion of the pathogenesis of CPTE in Japan. Consequently, the cases of CPTE diagnosed in past years might include different diseases. Furthermore, there are 2 concepts of CPTE: (1) PTE with a chronically unresolved thrombus in pulmonary artery, and (2) PTE with chronic pulmonary hypertension caused by an organized thrombus. In this study, we categorized PTE with chronic pulmonary hypertension into the CPTE group. Further investigation of CPTE with a precise definition is necessary to ascertain the reliability of our results.

When pulmonary thromboendarterectomy is not possible, the only curative therapy is lung transplantation. Organ transplant has recently become available as a treatment option in Japan, which makes it imperative to clarify the pathophysiology of CPTE in Japan so that lung transplantation for patients with CPTE can be considered as soon as possible.

Conclusions

The present study was conducted to investigate the incidence and clinical characteristics of patients with CPTE in Japan. There were some differences in the clinical characteristics of CPTE between Japanese and American patients, which suggests that the pathogenesis of CPTE in Japan may differ from that in the United States.

References


Appendix

The followings are the physicians/surgeons and clinical centers belonging to JaSPER.

Kazuhiko Abe: Chugoku-Rosai Hospital, Kure; Motomi Ando: Department of Thoracic Surgery, Fujita Health University, Toyoake; Sadahiro Asai: Sasebo City General Hospital, Sasebo; Masao Doi: Prefectural Hospital of Hiroshima, Hiroshima; Keigo Dote: Hiroshima City Asa Hospital, Hiroshima; Hiroyuki Fujieda: Matsuyama Municipal Hospital, Matsuyama; Satoru Fujita: Osaka Prefectural Hospital, Osaka; Hisayoshi Fujiwara: The Second Department of Medicine, Gifu University, Gifu; Nobuo Fukuda: Zentsuji National Hospital, Zentsuji; Yuji Hanafusa: Department of Cardiovascular Surgery, National Cardiovascular Center, Osaka; Shunnosuke Handa: Department of Internal Medicine, Tokai University, Isehara; Shinshuke Hiramatsu: Numazu City Hospital, Numazu; Katsuhiko Hiroshita: The Second Department of Internal Medicine, Keio University, Tokyo; Unosato Hara: Metropolitan Higashi-Matsudo Hospital, Matsudo; Tetsuo Hata: Department of Pulmonary Diseases/Infectious Diseases, Jikei University, Tokyo; Kazuhiko Hata: Department of Internal Medicine, Kansai University, Kakegawa; Tetsuya Hata: Ichinomiya City Hospital, Ichinomiya; Kiyokazu Ikeda: Okayama City Koyanagi Hospital, Okayama; Michihiro Inoue: The Second Department of Internal Medicine, Hiroshima University, Hiroshima; Ichiro Inoue: Hiroshima City Hospital, Hiroshima; Yoshiaki Ishigutsubo: Yokohama City Hospital, Yokohama; Kiniji Ishikawa: The First Department of Internal Medicine, Kinki University, Osaka; Junji Kanda: Asahi-chuoh Hospital, Chiba; Masakazu Kato: Tokyo-Koseinenkin Hospital, Tokyo; Ryo Katori: Showa General Hospital, Amagasaki; Kenjiro Kikuchi: The First Department of Medicine, Chiba Medical College, Chiba; Takao Kobayashi: Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, Hamamatsu; Kenichi Kodera: Tokyo Saiseikai Central Hospital, Tokyo; Shigeru Kohno: The Second Department of Internal Medicine, Nagasaki University, Nagasaki; Takeyoshi Kunieda: Department of Medicine, Utsunomiya Hospital, Tochigi; Ise: Masahiko Kurabayashi: The Second Department of Internal Medicine, Gunma University, Maebashi; Sachio Kuribayashi: Department of Radiology, Keio University, Tokyo; Takayuki Kuriyama: Department of Chest Medicine, Chiba University, Chiba; Jun Masuda: Akashi National Hospital, Akashi; Masahisa Masuda: The First department of Surgery, Chiba University, Chiba; Rokuro Matsuoka: Showa general Hospital, Tokyo; Masunori Matsuzaki: The Second Department of Internal Medicine, Yamaguchi University, Ube; Syoyo Misawa: Tokyo Medical Examiner's Office, Tokyo; Terumi Miyazawa: Hiroshima City Hospital, Hiroshima; Makoto Motou: The First Department of Surgery, Yokohama City University, Yokohama; Miho Motomizu: Komaki Citizen Hospital, Komaki; Shinichi Momomura: Toranomon Hospital, Tokyo; Noriyasu Morita: Gifu Municipal Hospital, Gifu; Shigefumi Moriioka: Kobe City General Hospital, Kobe; Shigefumi Moriioka: Kobe City General Hospital, Kobe; Takeshi Morishita: Ohfuna Central Hospital, Tokorozawa; Tokyo Metropolitan Hospital, Tokyo; Ryozo Nagai: Department of Cardiovascular Medicine, University of Tokyo, Tokyo; Itoku Nakagawa: Chugoku-Rosai Hospital, Kure; Takaomi Nakamoto: Department of Cardiology and Pneumology, Dokkyo University School of Medicine, Mibu; Norifumi Nakashita: Department of Internal Medicine, National Cardiovascular Center, Osaka; Takeshi Nakano: The First Department of Internal Medicine, Meiji University, Tsu; Masayuki Nakata: The First Department of Internal Medicine, Toho University, Tokyo; Masaharu Nishimura: The First Department of Internal Medicine, Hokkaido University, Sapporo; Akhiro Nishizawa: Musashino Red Cross Hospital, Musashino; Koji Nomura: Department of Cardiothoracic Surgery, Jikei University School of Medicine, Tokyo; Shigeaki Ogata: Kanagawa Prefectural Cardiovascular and Respiratory Center, Yokohama; Satoshi Ogawa: Department of Medicine, Keio University, Tokyo; Hiroshi Okteki: Saga Prefectural Hospital Koseikan, Saga; Minoru Okamoto: Kanazawa Medical Center, Kanazawa; Seiji Ogita: The Second Department of Surgery, Tottori University, Yonago; Kazuyoshi Sakai: Tosei General Hospital, Seto; Yoshishar Sakamoto: Department of Obstetrics and Gynecology, Nara Medical University, Nara; Hitoto Sakimoto: Chugoku-Rosai Hospital, Kure; Mamu Sakato: Sakai Municipal Hospital, Sakai; Takaoki Sato: Department of Cardiovascular Surgery, National Cardiovascular Center, Osaka; Harumi Sakurada: Metropolitan Hiroo General Hospital, Tokyo; Keichi Sato: Higashi-Matsudo Municipal Hospital, Matsudo; Tetsuo Satoh: Department of Pulmonary Diseases/Infectious Diseases, Jikei University, Tokyo; Keizo Shibata: Department of Internal Care Unit, Kanazawa University, Kanazawa; Tetsuya Shibuya: Ichinomiya City Hospital, Ichinomiya; Kiyokazu Shimizu: Hanaa City Hospital, Handa; Kunio Shirato: The First Department of Internal Medicine, Tohoku University, Sendai; Takeshi Sone: Ogaki Municipal Hospital, Ogaki; Takashi Suzuki: Prefectural Hospital of Hiroshima, Hiroshima; Tsuneaki Sugimoto: Kanto Central Hospital, Tokyo; Hidehara Suzuki: Department of Respiratory Internal Medicine, Showa University Fujisawa Hospital, Showa University, Yokohama; Masahiro Syakudo: Sumiyoshi Municipal Hospital, Osaka; Hiroyuki Tajima: Department of Radiology Medicine, Niigata Medical School, Toyo; Kenichi Takahashi: Yokohama-Minami-Kyosai Hospital, Yokohama; Ken Takakura: Nankai Hospital, Osaka; Ita; Shinichi Takamato: Department of Cardiovascular Surgery, University of Tokyo, Tokyo; Morimasa Takayama: Intensive and Coronary Care Unit, Niigata Medical School, Tokyo; Ken Takada: Department of Radiology, Mic University, Toyo; Kichi Tanaka: Miyoshi General Hospital, Miyoshi; Seiya Tsuchiya: Chikuma Hospital, Sakai; Junichi Udo: The First Department of Surgery, Kumamoto University, Kumamoto; Osamu Yanase: Tokyo Metropolitan Otsuka Hospital, Tokyo; Kiyoshi Yoshida: Department of Cardiology, Kawasaki Medical School, Kurashiki; Junichi Yoshikawa: The First Department of Internal Medicine, Osaka City University, Osaka; Masahiro Yoshimura: Imperial Cooperation Hospital, Toyo; Takeshi Yoda: Department of Pathology, National Cardiovascular Center, Osaka; Hideo Yoda: Department of Laboratory Medicine, Meiji University, Toyo; Sachio Watanabe: Gifu Prefectural Gifu Hospital, Gifu.