Recent Developments in Diagnostic Imaging Techniques and Management for Acute Pulmonary Embolism: Multicenter Registry by The Japanese Society of Pulmonary Embolism Research

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Abstract

Objective There are many reports on the diagnosis and management of acute pulmonary embolism (APE), but there have been no investigations concerning the actual conditions in which recent developments in diagnostic imaging techniques and therapies have been applied in clinical practice. The present study was designed to investigate the changes in diagnostic imaging techniques and therapies for APE.

Methods and Patients Three hundred and nine APE patients diagnosed during January 1994–October 1997 (Group 1) were compared with 257 APE patients diagnosed during November 1997–October 2000 (Group 2) in terms of the diagnostic imaging techniques and therapies for APE.

Results Compared with Group 1, pulmonary angiography and contrast-enhanced computed tomography were more frequently performed for diagnosis in Group 2 [45.3% vs 56.8% ($p=0.0069$) and 13.9% vs 57.6% ($p<0.0001$), respectively]. Heparin and vena cava filter were used more often in Group 2 [74.4% vs 82.1% ($p=0.033$) and 18.4% vs 33.9% ($p<0.0001$), respectively]. The frequency of thrombolytic therapy was unchanged between the two groups. Warfarin use in discharged patients increased from 71.9% to 83.8% ($p=0.0022$). However, the examination rates for deep vein thrombosis (DVT) were low (60.8% in Group 1 and 65.4% in Group

2, $p=0.29$) and unchanged using any imaging techniques.

Conclusion The diagnostic imaging techniques for APE increased in variety and the management has improved, while the diagnosis for DVT remains unchanged. (Internal Medicine 42: 470–476, 2003)

Key words: computed tomography, vena cava filter, heparin, thrombolytic therapy, warfarin, deep vein thrombosis

Introduction

The diagnosis and management for acute pulmonary embolism (APE) have changed in recent years. It is well-recognized that computed tomography (CT), especially helical CT (1–3) and electron beam tomography (4, 5), and magnetic resonance (MR) angiography (6) are useful for the diagnosis of APE. Most of the major hospitals in Japan are equipped with CT and MR. In the management of APE, temporal inferior vena caval filters can be used.

There are many reports on the diagnosis and management of APE (7, 8), but there have been no investigations concerning the actual conditions in which recent developments in diagnostic imaging techniques and therapies have been applied in clinical practice.

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(JaSPER) registered cases with pulmonary embolism during two periods (from January 1994 to October 1997 and from November 1997 to October 2000). The present study was designed to investigate the changes in diagnostic imaging techniques and therapies for APE, based on this registry.

Methods

Study population

The registry in the present study was conducted first between January 1994 to October 1997 and then between November 1997 to October 2000. In the first survey (9), a total of 533 consecutive Japanese patients with pulmonary embolism were registered from the participating centers in JaSPER (listed in the Appendix), and in the second, there were 373 patients. The diagnosis of pulmonary embolism was made either by a pulmonary angiogram, CT, or MR angiogram which indicated vessel occlusions or intraluminal filling defects, by a lung perfusion scan which indicated the high probability of pulmonary embolism, by transesophageal echocardiogram (TEE), or by an autopsy.

APE was defined as pulmonary embolism which occurs suddenly and we excluded the cases with a mean pulmonary artery pressure of over 40 mmHg without preexisting cardiac or pulmonary disease. There were 309 patients with APE between January 1994 and October 1997 (Group 1) and 257 between November 1997 and October 2000 (Group 2). For statistical analysis, the present study considered only those patients with APE.

All decisions concerning the diagnostic workup and treatment were made by the clinicians caring for each patient. The steering committee took every care not to influence the management strategy employed in the participating hospitals.

Data acquisition

Complete information on the clinical course and the diag-

nostic and therapeutic management of the patients entering the registry was obtained by means of a standardized questionnaire sent to the participating centers by the steering committee. Data were collected on 1) clinical symptoms and signs of the patients at diagnosis; 2) presence of underlying diseases or predisposing factors for APE; 3) definitive diagnostic procedures given to patients (pulmonary angiography, perfusion lung scan, contrast-enhanced CT, MR angiography, TEE, and autopsy, and in Group 2, also types of CT); 4) presence of deep venous thrombosis (DVT) and diagnostic procedures (contrast venography, venous ultrasonography, and radionuclide venography); 5) treatment given to patients (anticoagulation, thrombolysis, pulmonary embolectomy, catheter interventional therapy, and inferior vena cava filter implantation, and in Group 2, the types of filters); and 6) in-hospital clinical course.

Statistical analysis

Statistical analysis was carried out using StatView 5.0 (SAS Institute Inc). All continuous variables were expressed as mean±standard deviation and assessed by unpaired t-test. Comparisons of proportion were made by chi-square statistics or, when appropriate, by Fisher's exact test. Multiple logistic regression analysis was used to investigate the independent effect of multiple factors on remarkable facts. The results of the logistic regression models are presented as estimated odds ratios with the corresponding 95% confidence intervals. All significant tests were two-tailed, with $p < 0.05$ considered as statistically significant.

Results

The clinical backgrounds of patients with APE had no significant differences between Groups 1 and 2 (Table 1). The mean age of the patients at diagnosis was 59.9 ± 14.8 years in Group 1, and 60.3 ± 15.5 in Group 2 ($p = 0.70$). The overall in-

Table 1. Selected Characteristics at Diagnosis in Patients with Acute Pulmonary Embolism

Characteristics	Group 1 (n=309)	Group 2 (n=257)	p value
Age ≥ 65 years	137 (44.3%)	119 (46.3%)	0.67
Female	187 (60.5%)	162 (63.0%)	0.54
Cardiogenic shock	111 (35.9%)	79 (30.7%)	0.21
Recent major operation	110 (35.6%)	91 (35.4%)	>0.99
Recent major trauma or fracture	29 (9.4%)	20 (7.8%)	0.55
Cancer	70 (22.7%)	52 (20.2%)	0.53
Prolonged immobilization	71 (23.0%)	55 (21.4%)	0.69
Obesity (BMI ≥ 25.3)	106 (34.3%)	74 (28.8%)	0.17
Coagulopathy	17 (5.5%)	10 (3.9%)	0.43
Onset in hospital	145 (46.9%)	127 (49.4%)	0.61

Data presented are number (%) of patients. Recent major operation: any intraabdominal operation and all other operations lasting more than 45 minutes within a month, Recent major trauma or fracture: trauma or fracture involving the pelvis and lower extremities within a month, Prolonged immobilization: immobilization lasting at least 1 week, BMI: body mass index.

Figure 1. The number of uses of the three main imaging techniques (perfusion lung scan, pulmonary angiography and enhanced computed tomography) employed for diagnosis. 0, 1, 2 and 3 in this figure indicate the number of main diagnostic imaging techniques used. The distribution varied between Groups 1 and 2 ($p<0.0001$).

hospital mortality rate was 14.2% in Group 1 and 11.9% in Group 2 ($p=0.45$).

Diagnostic imaging techniques for APE

Perfusion lung scan was performed in 74.1% of Group 1 and in 76.7% of Group 2 ($p=0.50$), and ventilation scan in 28.2% of Group 1 and in 23.0% of Group 2 ($p=0.64$). Compared with Group 1, pulmonary angiography and contrast-enhanced CT were more frequently performed for diagnosis in Group 2 [45.3% vs 56.8% ($p=0.0069$) and 13.9% vs 57.6% ($p<0.0001$), respectively]. In Group 2, the type of CT in 66 patients (44.6% of patients underwent CT) was helical CT, and that in 3 patients (2.0%) was electron beam tomography. The use of MR angiography and TEE had increased (2.3% in Group 1 vs 6.2% in Group 2, $p=0.019$; 0.6% vs 3.9%, $p=0.015$, respectively).

The number of main imaging techniques (perfusion lung scan, pulmonary angiography and CT) used for diagnosis changed between Group 1 and 2 (Fig. 1). In cases that had undergone perfusion lung scan, pulmonary angiography and/or CT were performed in 45.9% of Group 1 and in

81.7% of Group 2 ($p<0.0001$). However, in cases that had not undergone perfusion lung scan, the frequency of pulmonary angiography and/or CT was unchanged between Group 1 and 2 (67.5% vs 75.0%, $p=0.36$).

Therapies for APE

Heparin was used more often in Group 2 (74.4% in Group 1 and 82.1% in Group 2, $p=0.033$). The frequency of thrombolytic therapy was unchanged between the two groups (50.2% in Group 1 vs 48.2% in Group 2, $p=0.67$). Catheter interventional therapy, percutaneous cardiopulmonary support, and surgical thrombectomy were unchanged between Group 1 and 2 (5.5% vs 5.8%, $p=0.86$; 1.6% vs 2.7%, $p=0.39$; and 2.3% vs 2.7%, $p=0.80$, respectively). Vena cava filters were used more often in Group 2 (18.4% in Group 1 and 33.9% in Group 2, $p<0.0001$). In Group 2, 53 patients (60.9% of patients used vena cava filters) were implanted with only the permanent type, 28 (32.2%) with the temporary type, and the temporary type was replaced with the permanent type in 6 (6.9%). Warfarin use in discharged patients increased from 71.9% to 83.8% ($p=0.0022$).

Diagnostic imaging techniques for DVT

The examination rates for DVT were not so high (60.8% in Group 1 and 65.4% in Group 2, $p=0.29$) and were unchanged by any of the imaging techniques in cases for which DVT was evaluated [venography (80.9% vs 73.2%, $p=0.10$), radionuclide venography (13.3% vs 11.9%, $p=0.75$) and venous ultrasonography (18.1% vs 23.8%, $p=0.19$)].

Relationship between vena cava filter, and examination of pulmonary angiography or evaluation of DVT

Vena cava filters were implanted in 37.8% of the patients that had undergone pulmonary angiography, and in 12.9% of the patients that did not ($p<0.0001$). The examination for DVT was carried out in 73.6% of patients implanted with vena cava filters, and in 57.8% of patients not implanted with filters ($p=0.0007$). Multi-factorial analysis revealed that the practice of pulmonary angiography was related to the implantation of vena cava filters and not to the period of examination, and that the use of vena cava filters was related to both the diagnostic procedures for DVT and the period of examination (Table 2).

Table 2. Results of Multiple-logistic Analysis (n=566)

The dependent variable	The independent variables	Odds ratio	95%CI	p value
PAG	Implantation of vena cava filter	3.91	2.55–5.99	<0.0001
	Group 2	1.33	0.94–1.89	0.11
Vena Cava filter	Examination of DVT	2.04	1.34–3.12	0.001
	Group 2	2.25	1.53–3.35	<0.0001

PAG: pulmonary angiography, DVT: deep vein thrombosis, CI: confidence interval.

Discussion

Diagnostic imaging techniques for venous thromboembolism have markedly progressed. The recognition of the disease appears to have increased. In the present study, we clarified the clinical state of APE in Japan by examining the progress in diagnostic imaging techniques and management.

Diagnosis of APE

Diagnostic imaging techniques have come to be used more aggressively. Especially, enhanced CT is used more frequently. Helical CT and electron beam tomography (1–5), which can be performed rapidly and have high resolution, have become popular and their sensitivity and specificity are not inferior to those of pulmonary angiography (1–5). Prospective studies showed that the sensitivity of helical CT ranged from 53% to 100% and the specificity from 81% to 100% (10). Moreover, CT is less invasive than pulmonary angiography and does not require special techniques. The increase in the use of CT may be due to these advantages.

In both examined periods, perfusion lung scan was performed in about three-fourths of the APE patients, and ventilation scan in about one-fourth. But, as shown in the results from PIOPET study (11), perfusion lung scan has a low specificity and is useful for a definite diagnosis only in limited cases.

Pulmonary angiography use for the diagnosis of APE also increased. This procedure is invasive but can be followed with catheter interventional therapy, including implantation of vena cava filter. Our results indicate the possibility that invasive implantation of vena cava filters may have augmented the use of pulmonary angiography for the diagnosis of APE. In the clinical situation, because management typically follows diagnosis, the idea that the method of management (or prophylaxis) would determine the method of diagnosis is somewhat unusual. But if it can be accepted that the trend toward the use of invasive trans-venous implantation of filter influences the use of pulmonary angiography, the period of occurrence of APE, that is, whether the patients with APE were in Group 1 or in Group 2, would not be related to the frequency of the use of pulmonary angiography (Table 2).

There are many reports about the usefulness of MR angiography for the diagnosis of APE (6). Lobar or segmental pulmonary embolism but not subsegmental embolism can be easily detected by MR angiography (6). In the present study, MR angiography came to be used more frequently, but was employed in only a small number of cases. MR angiography can be used for perfusion imaging (12), but not for patients with medical instruments affected by a strong magnetic field.

TEE is helpful to detect proximal pulmonary embolisms and its usefulness increases in the patients with cardiopulmonary arrest (13, 14) because other diagnostic techniques are difficult to use. As shown in the present study, TEE use, although increasing, is still rare.

Several imaging techniques are being used in combination

for the diagnosis of APE and this may lead to the increased use of each imaging technique. In the subgroup of patients who underwent perfusion lung scan, the practical rate of contrast-enhanced CT and/or pulmonary angiography is increasing recently, but in the subgroup of patients who did not undergo perfusion lung scan the practical rate of contrast-enhanced CT and/or pulmonary angiography did not increase. This suggests that lung perfusion scan is used as a screening procedure for the diagnosis of APE and that, in many recent cases, the diagnosis is confirmed by other imaging techniques after perfusion scan. This may be one of the reasons why contrast-enhanced CT and pulmonary angiography are used more frequently.

Management of APE

Anticoagulant therapy with intravenous heparin immediately after the onset of APE (15) and oral warfarin sodium are widely accepted for APE patients without contraindications (16, 17). Therefore, the recent increase in the use of these medicines appears reasonable. While thrombolytic therapy in clinically unstable cases or cases with overload of the right heart may be acceptable (18, 19), there is no clear evidence on the effectiveness of thrombolytic therapy in clinically stable cases without overload of the right heart. One-half of the patients were treated with thrombolytic therapy in both periods. The present study shows that the medical treatment for APE in Japan follows closely the generally accepted recommendations.

Vena cava filters were used more frequently than before. In Group 2, the temporary type increased by one-third in the use of filters. Vena cava filters may prevent re-embolization, which could otherwise lead to critical illness or death early after the onset of APE. Decousus et al showed in their randomized prospective trial that permanent vena cava filters prevented early recurrence of APE but increased chronic DVT (20). One of the reasons for the incremental use of temporary filters in patients with a temporary risk of venous thrombosis is that they protect against the early recurrence of APE without chronic adverse effects on the venous blood flow.

Catheter interventional therapy, percutaneous cardiopulmonary support and surgical embolectomy were used in a small number of the APE patients. But these therapies are important in the cases with cardiopulmonary arrest or in those that are clinically unstable, and may be useful for the patients with contraindications for thrombolysis (21–24). With increasing skill in catheter intervention, advances in the devices, and improving of cooperation with surgeons, these therapies will become widely used for patients who are too severe to benefit from the present system of management.

The selection of both diagnostic imaging techniques to be used and the type of management is greatly affected by the set-up ratio of each type of equipment and the severity of the illness. We could not examine the extent to which each institute that joined the registry possessed the various types of diagnostic equipment. But as shown in Table 1, the patient

characteristics were not different between Groups 1 and 2.

Mortality for APE

Mortality for APE was unchanged between the two periods. While the clinical diagnostic rate of APE in Japan was about one 200th that in the United States (25), the annual age-adjusted pulmonary embolism mortality per 100,000 persons in 1996 in Japan based on death certificates (0.7 among men and 0.8 among women (26)) was similar to that in non-white and non-black Americans (1.0 among men and 0.7 among women (27)) which is about one-third that in white Americans. In the clinical setting, the prevalence of APE in Asians was about one-fifth that in white Americans, showing the racial difference in the risk for APE (28). But the racial difference cannot completely explain the difference in the clinical diagnostic rate between Japan and America. A low ratio of correct diagnosis of patients with APE in Japan may also be a factor. Moreover, about 30–40% of the patients in this registry had cardiogenic shock, and this ratio is higher than in Western countries (29). It appears that the less severe cases of APE were under-diagnosed in Japan. If the diagnostic rate is elevated in the future, the mortality will appear to improve even without an actual change.

Imaging techniques of DVT

From the present results, some problems with the diagnosis of DVT in Japan appeared. First, the examination rates for DVT were low. Second, ultrasonographic techniques, which are non-invasive and have been recognized as useful, were used in only a minority of the patients.

DVT is well-known as one of the main causes of APE (29). But, as shown in previous reports, the detection rate of DVT and the frequency of the signs of DVT are low in Japan (9, 30). Therefore, physicians' interest in DVT is low in Japan and the level of research for DVT is also low. However, because one of the reasons for death from APE is acute recurrence, an increase in the detection of DVT may be needed to lower the mortality and, practically, to decide the indication for the use of vena cava filters.

Conclusion

The diagnostic imaging techniques for APE increased in variety and the management has improved, while the diagnosis for DVT remains unchanged.

Appendix

The leading members and their clinical centers belonging to JaSPER are listed as follows; Katsuya Akashi: Department of Emergency Medicine, St. Marianna University School of Medicine, Kawasaki; Motomi Ando: Department of Thoracic Surgery, Fujita Health University, Toyoake; Sadahiro Asai: Sasebo City General Hospital, Sasebo; Hirofumi Fujioka: Hakusan Clinic, Hakusan; Satoru Fujita: Takarazuka Daiichi Hospital, Takarazuka; Hisayoshi Fujiwara: The Second Department of Medicine, Gifu University,

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