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Clinical Characteristics, Diagnosis and Management of Patients With Pulmonary Thromboembolism Who are Not Diagnosed in the Acute Phase and Not Classified as Chronic Thromboembolic Pulmonary Hypertension

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Background There have been many cases of pulmonary thromboembolism (PTE) that were not diagnosed in the acute phase and not classified as chronic thromboembolic pulmonary hypertension (CTEPH). The aim of the present study was clarify the clinical characteristics of chronic PTE.

Methods and Results The study subjects were 601 patients (chronic PTE=92, acute PTE=456, CTEPH=53) who were clinically diagnosed before their death. Dyspnea and chest pain, which are frequently found in acute PTE, were found less frequently in chronic PTE. The diagnosis of chronic PTE is often delayed in cases of mild to moderate severity with atypical onset. Chronic heart failure and chronic respiratory failure were most frequent in chronic PTE, and cerebrovascular disease was present in approximately 15% of the cases of chronic PTE. Pulmonary angiography and ventilation lung scan were used least frequently in acute PTE. Heparin and thrombolysis were used most frequently in acute PTE.

Conclusions Besides the atypical onset and reduced severity, the presence of preexisting diseases may be one of the reasons why the diagnosis for chronic PTE is delayed. The diagnostic and management techniques differ according to the type of PTE. (*Circ J* 2005; **69:** 1009 – 1015)

Key Words: Filter; Heparin; Pulmonary hypertension; Thrombolysis

Acute pulmonary thromboembolism (PTE) has been diagnosed more often in recent years in Japan[1–3] and chronic thromboembolic pulmonary hypertension (CTEPH) represents a relatively greater percentage of PTE cases in Japan than in Western countries[4,5] Acute PTE and CTEPH are well-defined[6–8] and the diagnosis and management have been discussed separately, but there are many PTE cases that have not been classified as acute PTE or CTEPH.

We define unclassified cases that can not be categorized into CTEPH but have some chronic factor, according to the attending physician's judgment, as chronic PTE. It is clinically important to clarify the reason why the cases with chronic PTE are not diagnosed in the acute phase. We hypothesized that one reason was the differences in the clinical characteristics of the types of PTE. There have been no reports that examined the clinical characteristics of chronic PTE, so our main aim was to do this. We also examined the differences in diagnostic methods and management of the 3 types of PTE (acute PTE, chronic PTE and CTEPH).

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Methods

Study Population

We used the data from the third registry of the Japanese Society of Pulmonary Embolism Research (JaSPER), in which 629 patients with pulmonary embolism are enrolled. The study protocol was approved by the human research committee of Tohoku University School of Medicine. Acute PTE (461 patients, 73.3%) was defined as acute onset illness of less than 2 weeks; CTEPH (53 patients, 8.4%) was defined as having stable pulmonary thromboembolic lesions for 6 months or longer, a mean pulmonary artery pressure >25 mmHg, and pulmonary capillary wedge pressure <12 mmHg[7,8] Ninety-two patients (14.6%) were classified as chronic PTE because they did not satisfy the criteria for either acute PTE or CTEPH and these cases included the subacute type in which the acute onset of PTE is diagnosed late, and acute-with-chronic type in which the patient complains of slight symptoms for a long time before having an

Table 1 Clinical Characteristics of Pulmonary Thromboembolism

	Acute PTE (n=456)	Chronic PTE (n=92)	CTEPH (n=53)
Age (years)	66±16	65±16	57±15*,†
BMI[#1]	24.4±4.2	23.8±3.0	23.0±3.8*
Female	287 (62.9%)	50 (54.3%)	32 (60.4%)
Days from onset of symptom to diagnosis[#2]	1	16.5*	246*,†
Death 30-days after diagnosis	30 (6.6%)	6 (6.5%)[#3]	1 (1.9%)

*PTE, pulmonary thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension; BMI, body mass index. [#1]361 patients with acute PTE, 73 with chronic PTE and 48 with CTEPH. [#2]Median, [#3]Two cases died from recurrence of PTE, 2 from chronic respiratory failure, and the remaining 2 from cancer. *p<0.05 vs acute PTE, †p<0.05 vs chronic PTE.*

Table 2 Acute Episodes and Symptoms of Pulmonary Thromboembolism

	Acute PTE	Chronic PTE	CTEPH	p-value
Acute episodes[#1]				
None	12 (2.8%)	35 (47.3%)	18 (47.4%)	
Once (this time)	382 (87.8%)	12 (16.2%)	7 (18.4%)	
Once (past)	4 (0.9%)	4 (5.4%)	2 (5.3%)	
Twice or more	37 (8.5%)	23 (31.1%)	11 (28.9%)	<0.001
Symptoms				
Dyspnea	371/445 (83.4%)	67/90 (74.4%)	50/53 (94.3%)	0.008
Chest pain	144/444 (32.4%)	15/90 (16.7%)	11/53 (20.8%)	0.004
Cold sweat	96/445 (21.6%)	7/89 (7.9%)	6/53 (11.3%)	0.004
Cough	46/443 (10.4%)	11/89 (12.4%)	10/53 (18.9%)	0.18
Hemoptysis	16/443 (3.6%)	4/89 (4.5%)	6/53 (11.3%)	0.04
Fever	32/441 (7.3%)	6/89 (6.7%)	4/52 (7.7%)	0.98
Palpitation	93/443 (21.0%)	10/89 (11.2%)	13/52 (25.0%)	0.07
Syncope	92/444 (20.7%)	7/90 (7.8%)	3/53 (5.7%)	0.001
Onset in hospital	185/456 (40.6%)	17/91 (18.7%)	0/53 (0.0%)	<0.001

See Table 1 for abbreviations. [#1]435 acute PTE, 74 in chronic PTE, and 38 CTEPH.

Table 3 Risk Factors for Pulmonary Thromboembolism

	Acute PTE (n=456)	Chronic PTE (n=90)	CTEPH (n=53)	p-value
Prolonged immobilization	129 (28.3%)	15 (16.7%)	0 (0.0%)	<0.001
Recent major operation	111 (24.3%)	2 (2.2%)	2 (3.8%)	<0.001
Recent trauma	24 (5.3%)	5 (5.6%)	1 (1.9%)	0.55
Recent fracture	40 (8.8%)	4 (4.4%)	0 (0.0%)	0.04
Active cancer	95 (20.8%)	12 (13.3%)	4 (7.5%)	0.02
Chronic heart failure	29 (6.4%)	15 (16.7%)	5 (9.4%)	0.005
Chronic respiratory failure	15 (3.3%)	9 (10.1%)	3 (5.7%)	0.02
Cerebrovascular disease	45 (9.9%)	14 (15.4%)	2 (3.8%)	0.08

See Table 1 for abbreviations.

acute episode of PTE. Finally, 23 patients (3.7%) remained unclassified because the participating doctor could not decide what type of PTE best described the patient. All cases were diagnosed between November 2000 and August 2003 in the participating centers in JaSPER listed in Appendix 1. The diagnosis of pulmonary embolism was made either by pulmonary angiogram, computed tomography (CT), or magnetic resonance angiogram, which indicated vessel occlusions or intraluminal filling defects, by lung perfusion scan, which indicated a high probability of pulmonary embolism, by trans-esophageal echocardiogram, which indicated central pulmonary emboli, or by autopsy, which demonstrated any pulmonary emboli.

Acute PTE was not been diagnosed before autopsy in 5 patients. Our study used the data from 456 patients with acute PTE, excluding these 5 patients, 92 patients with chronic PTE, and 53 patients with CTEPH. Their clinical characteristics are shown in Table 1.

All decisions concerning the diagnostic workup, treatment, and cause of death whether from a first acute PTE attack or recurrent PTE were made by the clinicians caring for each patient. The steering committee took care not to influence the management strategy used in the participating hospitals.

Data Acquisition

Complete information on the clinical course and the diagnostic and therapeutic modalities of the patients entering the registry was obtained from a standardized questionnaire sent to the participating centers by the steering committee. Data were collected on (1) the type of PTE (acute PTE, chronic PTE, CTEPH, or unclassified); (2) 30-day mortality after the diagnosis of PTE; (3) clinical symptoms and signs at diagnosis; (4) presence of underlying diseases or predisposing factors for PTE; (5) definitive diagnostic procedures; and (6) treatment.

Table 4 Diagnostic Techniques Used for Pulmonary Thromboembolism

	Acute PTE (n=452)	Chronic PTE (n=92)	CTEPH (n=52)	p-value
Pulmonary angiography	165 (36.5%)	38 (41.3%)	28 (53.8%)	0.04
Perfusion lung scan	280 (61.9%)	71 (77.2%)	40 (76.9%)	0.004
Ventilation lung scan	83 (18.4%)	32 (34.8%)	17 (32.7%)	<0.001
CT	280 (61.9%)	66 (71.7%)	35 (67.3%)	0.18
MRI	7 (1.5%)	3 (3.3%)	3 (5.8%)	0.11
D-dimer	352 (77.9%)	76 (82.6%)	47 (92.2%)[#1]	0.04
DVT assessment	381 (84.3%)	76 (82.6%)	46 (88.5%)	0.64

The presence of deep vein thrombosis (DVT) was determined by lower limb compression venous ultrasonography, computed tomography (CT), contrast venography, radio-isotope venography or magnetic resonance imaging (MRI). [#1]This population was 51. See Table 1 for other abbreviations.

Table 5 Diagnostic Techniques Used for Deep Vein Thrombosis

	Acute PTE (n=381)	Chronic PTE (n=76)	CTEPH (n=46)	p-value
Contrast venography	155 (40.7%)	21 (27.6%)	20 (43.5%)	0.08
CT	115 (30.2%)	35 (46.1%)	17 (37.0%)	0.02
US	208 (54.6%)	52 (68.4%)	31 (67.4%)	0.03
MRI	15 (3.9%)	4 (5.3%)	4 (8.3%)	0.37
RI venography	18 (4.7%)	2 (2.6%)	2 (4.3%)	0.72

US, lower limb venous compression ultrasonography; RI, radio-isotope. See Tables 1 and 4 for other abbreviations.

Table 6 Management of Pulmonary Thromboembolism

	Acute PTE (n=456)	Chronic PTE (n=87)	CTEPH (n=53)	p-value
Heparin	424 (93.0%)	60 (69.0%)	30 (56.6%)	<0.001
Thrombolysis	269 (59.0%)	29 (33.3%)	23 (43.4%)	<0.001
Urokinase	191 (41.9%)	24 (27.6%)	16 (30.2%)	0.02
t-PA	149 (32.7%)	5 (5.7%)	13 (24.5%)	<0.001
IVC filter[#1]	161 (35.3%)	23 (26.4%)	20 (37.7%)	0.24
Permanent type	85 (18.6%)	17 (19.5%)	17 (32.1%)	0.07
Temporary type	69 (15.1%)	6 (6.9%)	5 (9.4%)	0.08
Retrievable type	23 (5.0%)	1 (1.1%)	0 (0.0%)	0.07
PCPS	38 (8.3%)	2 (2.3%)	3 (5.7%)	0.12
Surgery	10 (2.2%)	1 (1.1%)	13 (24.5%)	<0.001
Catheter therapy	48 (10.5%)	2 (2.3%)	3 (5.7%)	0.03
Warfarin[#2]	349 (81.9%)	70 (87.5%)	47 (90.4%)	0.18

t-PA, tissue plasminogen activator; IVC, inferior vena cava; PCPS, percutaneous cardiopulmonary support. See Table 1 for other abbreviations. Surgery in acute PTE and chronic PTE was surgical embolectomy, and that in CTEPH was thromboendarterectomy. [#1]In 16 cases (9.9%) of acute PTE, 1 case (4.3%) of chronic PTE, and 2 cases (10.0%) of CTEPH, 2 types of IVC filter were used. [#2]Cases who died or were transfered to another hospital within 30 days were excluded and this population was 426 acute PTE, 80 chroni cPTE and 52 CTEPH.

Statistical Analysis

Statistical analysis was carried out using SPSS 12.0 (SPSS Inc, Chicago, ILL, USA). All continuous variables were analyzed by Mann-Whitney test and expressed as mean ± standard deviation or median. Categorical data were analyzed by chi-square statistics. Multiple comparisons were performed using Bonferroni's method. All significant tests were two-tailed.

Results

Clinical Characteristics

Patients with CTEPH were the youngest and had the smallest body mass index among the 3 types of PTE. Days from onset of symptoms to diagnosis were shorter in acute PTE, chronic PTE, and CTEPH in this order. The cause of death of the patients with acute PTE was PTE in 76.7%, preexisting disease in 13.3%, and intracranial hemorrhage in 10.0% and 33.3%, 66.7%, and 0.0%, respectively for chronic PTE (p=0.015) (Table 1).

Most of the patients with acute PTE had one acute episode. Although half of the cases with either chronic PTE

Table 7 Concentration of D-Dimer and Subsequent Management Technique

	D-dimer		p-value
	≥0.5 μg/ml	<0.5 μg/ml	
Chronic PTE			
Heparin	75.4%	53.3%	0.12
Thrombolysis	40.4%	26.7%	0.38
CTEPH			
Heparin	73.5%	23.1%	0.003
Thrombolysis	58.8%	23.1%	0.049

See Table 1 for abbreviations.

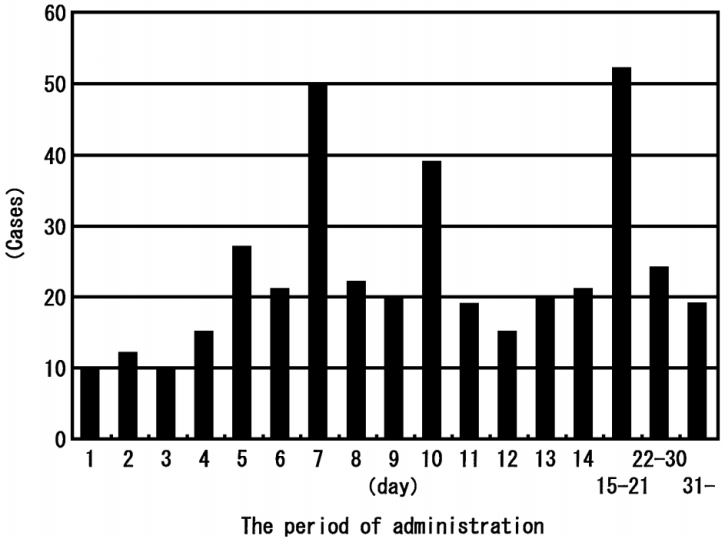

Fig 1. Duration of heparin administration in patients with acute pulmonary thromboembolism (median = 10 days).

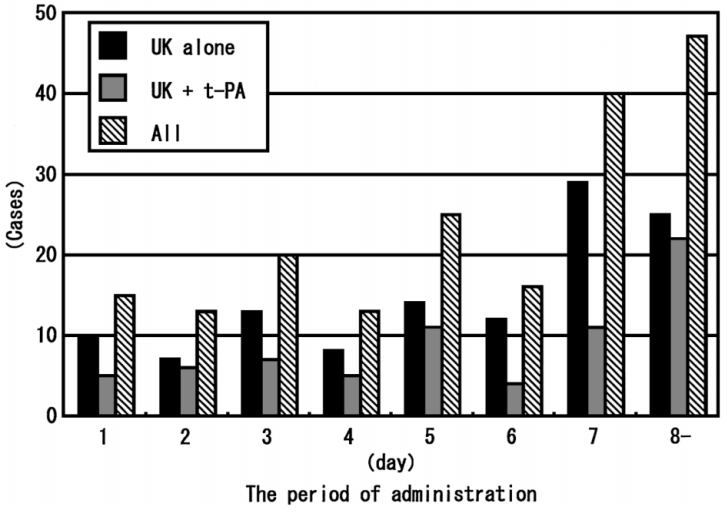

Fig 2. Duration of urokinase (UK) administration in patients with acute pulmonary thromboembolism. There were no statistical differences between the periods of UK alone and UK with tissue plasminogen-activator (t-PA) (p=0.16). The median value of UK administration was 6 days.

or CTEPH did not have acute episodes, approximately 30% had suffered repeated acute episodes Chest pain, cold sweat and syncope were the most frequent symptoms in acute PTE, whereas dyspnea and hemoptysis were the most frequent in CTEPH (Table 2).

As risk factors, prolonged immobilization, recent major operation, recent fracture and active cancer were most frequent in acute PTE, whereas chronic heart or respiratory failure was most frequent in chronic PTE. Cerebrovascular disease was present in approximately 15% of chronic PTE, but this ratio was not significant (Table 3): 33 cases of chronic PTE (35.9%) had chronic heart failure, chronic respiratory failure or cerebrovascular disease.

Shock or cardiopulmonary arrest at diagnosis occurred in 21.8% of acute PTE, 1.1% of chronic PTE, and 1.9% of CTEPH ($p<0.001$).

Diagnostic Techniques

Pulmonary angiography, perfusion lung scan and ventilation lung scan were used least frequently in acute PTE. D-dimer was examined most frequently in CTEPH and a high concentration (≥0.5 μg/ml) was found in 96.0% in acute PTE, 78.9% in chronic PTE, and 72.3% in CTEPH ($p<0.001$). Deep vein thrombosis (DVT) was assessed in over 80% of each type of PTE (Table 4).

CT and lower limb venous compression ultrasonography were used for detecting DVT least frequently in acute PTE (Table 5). Symptoms of DVT were present in 38.5% of acute PTE, 32.1% of chronic PTE, and 27.5% of CTEPH ($p=0.21$). The actual presence of DVT was 65.2% in acute PTE, 52.4% in chronic PTE, and 48.9% in CTEPH ($p=0.02$). DVT was examined in 39.9% and 15.2%, and found in 84.6% and 87.5% of cases of acute PTE on the day it was diagnosed or the next day, respectively.

Management

Heparin, thrombolysis and catheter therapy were used most frequently in acute PTE, whereas surgery was chosen most frequently in CTEPH. The surgery in acute PTE and chronic PTE was embolectomy, and that in CTEPH was thromboendarterectomy. Inferior vena cava filters were used in approximately 30% of each type of PTE. In the cases that survived 30 days, warfarin was used in over 80% regardless of the type (Table 6).

Patients with a high concentration of D-dimer were administered heparin and thrombolytic agents more frequently in CTEPH and chronic PTE cases, but there was no significant difference in chronic PTE (Table 7).

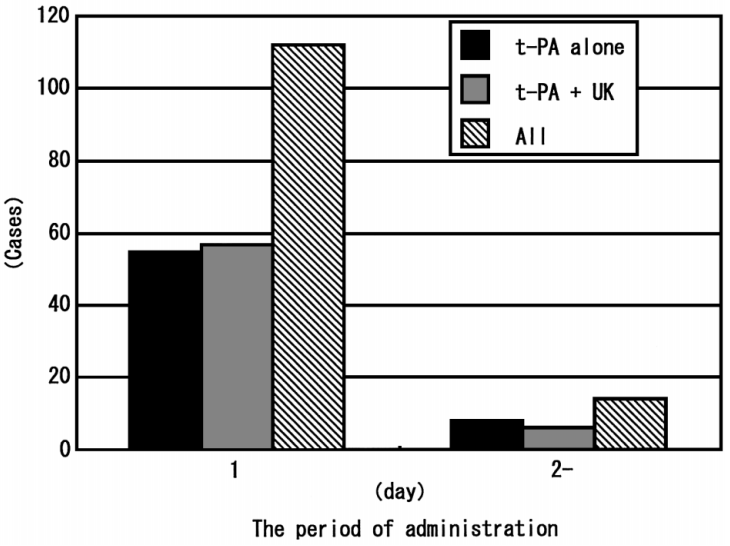

Fig 3. Duration of tissue plasminogen-activator (t-PA) use in patients with acute pulmonary thromboembolism. There were no statistical differences between the administered periods of t-PA alone and that of t-PA with urokinase (UK) (p=0.79). The median value of t-PA administration was 1 day.

In acute PTE, the median duration of heparin administration was 10 days (Fig 1). Both urokinase and tissue plasminogen activator (t-PA) were used in 26.4% (71 patients) of cases treated with thrombolytic agents, which means that these combinations were used 37.2% in patients administered urokinase, and 47.7% in those given t-PA. The day of starting these was the same in 70.6% of the cases administered both medicines. There was no significant differences in the duration of urokinase use between cases with and those without t-PA, and the median duration was 6 days (Fig 2). There were also no significant differences in the duration of t-PA use between cases with and without urokinase, and the median duration was 1 day (Fig 3).

Discussion

In the present study, we showed that chronic PTE was characterized by (1) different symptoms to those in acute PTE, (2) delayed clinical diagnosis, (3) presence of chronic heart and chronic respiratory failure, (4) lower rate of symptoms similar to those found in acute PTE, and (5) mild to moderate severity of PTE. We also found that the diagnostic and management techniques differed according to the type of PTE.

Clinical Characteristics

There are many studies on typical acute PTE[1,3,5,6,9–11] and CTEPH,[12–15] but none of cases other than these 2 types. In the present study, cases that could not be categorized into acute PTE or CTEPH and had some chronic factors were defined as chronic PTE and we then compared the clinical characteristics of these 3 types of PTE (acute PTE, chronic PTE and CTEPH). Some investigators have suggested that CTEPH occurs by different mechanisms from those of acute PTE,[14] but another aspect is that neither chronic PTE nor CTEPH was detected in the acute phase. Therefore, to determine the clinical characteristics of chronic PTE and CTEPH it was necessary to clarify why the diagnosis was delayed.

As shown in Table 1, chronic PTE is not usually accompanied by the sudden appearance of symptoms as in acute PTE and many of the chronic PTE cases had delayed diagnosis. When comparing the 3 types of PTE in terms of the risk, prolonged immobilization, recent major surgery, fracture, and cancer were found most frequently in acute PTE, whereas many patients with chronic PTE had chronic heart or respiratory failure. Therefore, the presence of these preexisting diseases seems to be one of the reasons why the diagnosis for chronic PTE is delayed. Approximately 20% of the chronic PTE cases occurred in hospital, which shows that acute risk factors also contributed to the occurrence of chronic PTE in some cases. The 30-day mortality in chronic PTE was similar to that in acute PTE, but many of the deaths in chronic PTE patients were caused not by PTE itself but by the preexisting disease.

Patients with CTEPH were the youngest and had the lowest body mass index among the 3 types of PTE, which is consistent with the findings of a previous report[15] and may indicate that the mechanisms of CTEPH are different from those for acute PTE. Further studies are needed to confirm this hypothesis. Our data showed that CTEPH comprises a high percentage (8.4%) of PTE cases compared with that in Western countries but was not as high as described previously.[4,5] Moreover, 50% of the CTEPH patients did not have acute episodes, which suggests that CTEPH did not always follow acute PTE.

As symptoms, dyspnea, chest pain and cold sweat occurred at the lowest rate in chronic PTE, whereas dyspnea was highest in CTEPH, and chest pain, cold sweat and syncope were highest in acute PTE. Delays in the diagnosis of chronic PTE appear to be partly because of the low incidence of the subjective findings of typical acute PTE.

Diagnostic Techniques

The diagnostic techniques were not uniform for the 3 types of PTE and were chosen according to the type of PTE. This difference in diagnostic approach may be related to the severity of PTE and to the need to examine the indication for therapy. For example, pulmonary angiography was performed more frequently in CTEPH because of the definition of the indication for thromboendartectomy. Ventilation and perfusion lung scans were used more in chronic PTE and CTEPH. However, only a few hospitals in Japan can perform a ventilation scan on the day it is ordered. We previously reported that perfusion and ventilation lung scans were chosen in the less severe cases of acute PTE,[6] and because there is more time for diagnosis in cases of

chronic PTE and CTEPH, lung scans were chosen more frequently for these 2 types of PTE. CT was used in all types of PTE. Technical developments in multidetector row CT have increased its effectiveness for the diagnosis of PTE, and lesions at the subsegmental pulmonary artery can be detected![16,17] Therefore, it is expected that CT diagnosis will be used more often.

Though the concentrations of D-dimer were highest in acute PTE, the rate of investigating this parameter was highest in CTEPH. Patients with CTEPH had right ventricular overload, which may be a decision criteria for trying thrombolytic therapy in acute PTE, but in CTEPH, it has to be determined whether the acute thromboembolic factor contributed to the patient's clinical status. That is, the use of D-dimer in patients with CTEPH may not be useful for the diagnosis of PTE but rather for therapeutic selection.

A low rate of assessing DVT is a clinical problem in acute PTE in Japan[4,5,9,18] and it is found less in patients with acute PTE in Japan than in Western countries[9,18] But, in the present study DVT was found in more than 80% when diagnosis was limited to the cases either examined for DVT on the day when acute PTE was diagnosed, or on the next day. This fact shows that examination for DVT early after the acute PTE diagnosis is necessary for accurate estimation of the DVT frequency in Japan. CT and lower limb venous compression ultrasonography are widely used to diagnose DVT[18] and PTE can be diagnosed almost simultaneously.

Management

The management tecnique also differed among the 3 types of PTE. Heparin, thrombolysis and catheter therapy were used more often in acute PTE, and surgery more often in CTEPH. The surgery in CTEPH was thromboendarterectomy and for acute and chronic PTE it was thrombectomy. Inferior vena cava filters and warfarin were used regardless of the type of PTE. The permanent type of filter tended to be used in CTEPH and both temporary and retrievable types were used in acute PTE, but the differences did not reach statistical significance. However, because permanent inferior vena cava filters increase the occurrence of DVT![19,20] their selection has to be made carefully. Pulmonary hypertension is thought to be a permanent risk factor for PTE, so the permanent type of filter might be chosen for CTEPH. As for anticoagulation, warfarin was used from the start of therapy without the use of heparin in some cases with chronic PTE and CTEPH.

In acute PTE, urokinase was used with and without t-PA. The duration of urokinase use was 6 days, regardless of the use of t-PA. The duration of t-PA use was 1 day, regardless of the use of urokinase. The Food and Drug Administration in the United States approves the use of only 100 mg t-PA/2 h for acute PTE![21] In practice, the duration of thrombolytic agent use in Japan differs from that in the USA and varies according to the patient (Figs 2,3). It should be noted that 25% of the cases in which thrombolysis was used both urokinase and t-PA were administered. The combination is an empirical administration method for decreasing residual thrombosis and improving the quality of life in the long term. Further studies are needed to objectively assess the effectiveness of the combined use of urokinase and t-PA.

When the concentration of D-dimer was 0.5 μg/ml or higher in chronic PTE and CTEPH, heparin and thrombolysis were used more often, but the difference was significant only in CTEPH. This suggested that, in cases with CTEPH already known to have right ventricular overload, D-dimer may be a useful tool for deciding whether to use thrombolytic agents.

Conclusion

Many of the cases with chronic PTE did not have typical acute episodes of PTE, nor was their onset defined. The severity of PTE in most cases of chronic PTE was mild to moderate. Dyspnea and chest pain, which are frequently found in acute PTE, were found less frequently in chronic PTE. Besides these findings, the presence of preexisting diseases, including chronic heart and respiratory failure, may contribute to the delayed diagnosis ofn chronic PTE. Perfusion lung scans were used most frequently in chronic PTE and thrombolysis was used less frequently.

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Appendix 1

The following centers participated in the third registry of JaSPER.
Second Department of Internal Medicine, Akita University, Akita; Department of Respirology, Graduate School of Medicine, Chiba University, Chiba; Department of Cardiology and Pneumology, Dokkyo University School of Medicine, Mibu; Department of Pulmonary Medicine, Fukushima Medical University, Fukushima; Ichinomiya City Hospital, Ichinomiya; Izumi City Hospital, Osaka; Department of Surgery, Jichi Medical School, Minamikawachi; Department of Thoracic and Cardiovascular Surgery, Kanazawa Medical University, Ishikawa; Department of Medicine, Keio University, Tokyo; Department of Anesthesiology, Kitazato University, Sagamihara; Division of Cardiovascular and Respiratory Medicine, Graduate School of Medicine, Kobe University, Kobe; Metropolitan Hiroo General Hospital, Tokyo; Mie Prefectural General Medical Center, Yokkaichi; The First Department of Internal Medicine, Mie University, Tsu; Musashino Red Cross Hospital, Musashino; Second Department of Internal Medicine, Nagasaki University, Nagasaki; Department of Anesthesiology, Nara Medical School, Kashihara; Narita Red Cross Hospital, Narita; Intensive and Coronary Care Unit, Nippon Medical School, Tokyo; Saka General Hospital, Shiogama; Sasebo City General Hospital, Sasebo; Seirei Mikatahara General Hospital, Hamamatsu; Sendai Open Hospital, Sendai; Department of Respiratory Internal Medicine, Showa University Fujisawa Hospital, Showa University, Yokohama; Department of Cardiology, St Marianna University School of Medicine, Kawasaki; Tachikawa Kyosai Hospital, Tachikawa; Department of Cardiology, Toho University Omori Hospital, Toho University, Tokyo; Respiratory Center, Toho University Omori Hospital, Toho University Tokyo; Department of Cardiovascular Medicine, Graduate School of Medicine, Tohoku University, Sendai; Tokyo Teishin Hospital, Tokyo; Toranomon Hospital, Tokyo; Division of Organ Regeneration Surgery, Tottori University, Yonago; Department of Cardiovascular Surgery, Graduate School of Medicine, University of Tokyo, Tokyo; The First Department of Internal Medicine, Yamagata University, Yamagata.