Pulmonary Embolism is an Important Cause of Death in Young Adults

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Background Population-based analysis shows that deaths from pulmonary embolism (PE) are increasing in the older age groups, but it is unclear to what degree PE contributes to death in different ages and gender.

Methods and Results Potential contribution factors for all PE and for critical PE (in which PE was the primary cause of death or the main diagnosis) were examined in 396,982 autopsy cases. For all PE, odds ratio (OR) in males was 0.61 (95% confidence interval (CI) 0.59–0.64, p<0.0001), compared with that in females. ORs were 1.10 (95% CI 1.05–1.14, p<0.0001) in 1991–1994 and 1.19 (95% CI 1.14–1.25, p<0.0001) in 1995–1998, compared with those in 1987–1990. ORs for ages 0–9 and 40+ were significantly low compared with that for ages 20–39. For critical PE, similar results were obtained. Pregnancy and/or delivery were found in 38.5% in cases of critical PE in females aged 20–39.

Conclusion Compared with other age groups, PE contributed more to deaths in those aged 20–39 years. In recent years, deaths from PE have been slightly but significantly increasing. The incidence of clinically diagnosed critical PE also has been increasing. (*Circ J* 2007; **71:** 1765–1770)

Key Words: Age; Delivery; Pregnancy; Pulmonary embolism

The number of deaths from pulmonary embolism (PE) has been increasing in Japan[1] and the incidence of PE in autopsy cases is also reported to have increased from 1958 to 1986[2,3] Population-based analysis shows that deaths from PE are increasing in older age groups but PE is often misdiagnosed[4,5]

There are no reports on the incidence of PE in autopsy cases after 1986 in Japan and the following remain to be solved: (1) to what degree does PE contribute to death in different ages and genders and (2) what factor(s) contributes to diagnosis of PE before death. Therefore, our aims in the present study were to examine the incidence of PE in autopsy cases after 1986, and to clarify these 2 unsolved questions.

Methods

The subjects of the present study included PE cases confirmed by autopsy in Japan between 1987 and 1998[6–17] We excluded cases of pulmonary microembolism with disseminated intravascular coagulation from our analysis. PE was defined as critical (critical PE) when it was the primary cause of death or the main diagnosis and it includes all types of PE. The term "all PE" was used to indicate the total number of thrombotic PEs, tumor PEs, bacterial PEs, mycotic PEs and other emboli (eg, fat, amniotic fluid, etc)[18] To make it possible to compare our data with those reported by Mieno et al[3] we analyzed our PE cases according to Mieno's criteria in which cases less than 1 year old and those with non-thrombotic PE were excluded.

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 (SPSS Inc, Chicago, IL, USA). Non-ordinal categorical data using the chi-square test. The results of the logistic regression models and Poisson regression analysis[19] are presented as estimated odds ratios (ORs) with the corresponding 95% confidence intervals (CIs).

Table 1 Embolic Source (n=11,367)

	n (%)
Thrombus	*10,369 (91.2)*
Tumor	*503 (4.4)*
Bacterial or fungal	*247 (2.2)*
Bone marrow	*143 (1.3)*
Fat	*124 (1.1)*
Amnionic fluid	*49 (0.4)*
*Others**	*25 (0.2)*

Some cases had 2 or more sources.

**Air in 8 cases, cholesterin crystal in 6, contrast medium in 2, bone meal in 2 (both after bone fracture), foreign body in 2, and bile, amebic abscess, amyloid, ovum of paracsite, and compression from the aorta in 1 case each.*

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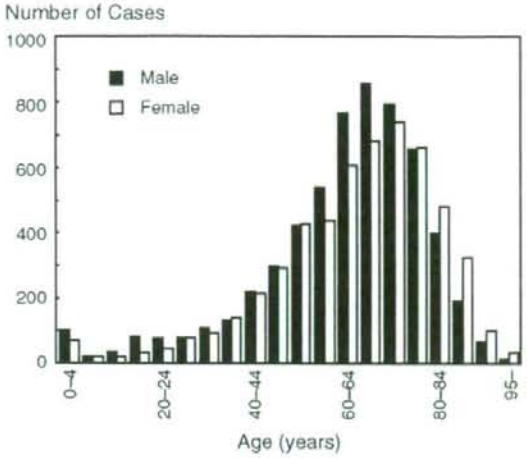

Fig 1. Distribution of autopsy cases with all pulmonary embolisms.

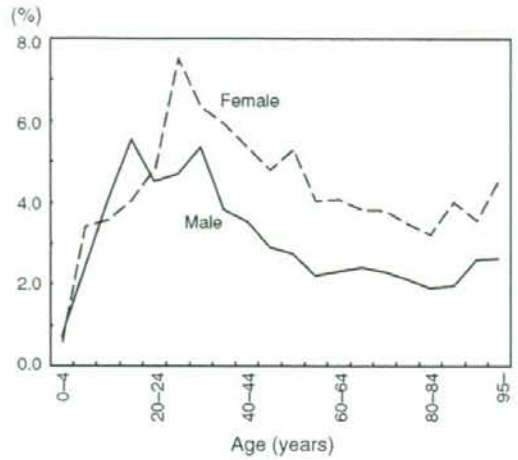

Fig 2. Ratio of autopsy cases of all pulmonary embolism by age (5-year groups) and gender.

Table 2 Number of Cases of PE in Autopsies by Years

Year	No. autopsies	All PE, n (%)	Thrombotic PE, n (%)	Critical PE, n (%)	Clinically diagnosed critical PE, n (%)
1987	39,399	1,169 (2.97)	1,063 (2.70)	336 (0.85)	46 (13.69)
1988	39,333	1,028 (2.61)	939 (2.39)	318 (0.81)	48 (15.09)
1989	38,439	972 (2.53)	895 (2.33)	299 (0.78)	44 (14.72)
1990	38,288	980 (2.56)	885 (2.31)	347 (0.91)	55 (15.85)
1991	36,474	1,141 (3.13)	1,047 (2.87)	430 (1.18)	71 (16.51)
1992	34,071	889 (2.61)	797 (2.34)	356 (1.04)	76 (21.35)
1993	31,949	1,030 (3.22)	946 (2.96)	419 (1.31)	72 (17.18)
1994	28,563	726 (2.54)	657 (2.30)	310 (1.09)	43 (13.87)
1995	28,682	899 (3.13)	813 (2.83)	426 (1.49)	81 (19.01)
1996	27,774	796 (2.87)	743 (2.68)	353 (1.27)	71 (20.11)
1997	27,391	857 (3.13)	781 (2.85)	370 (1.35)	81 (21.89)
1998	26,619	880 (3.31)	803 (3.02)	399 (1.50)	88 (22.06)

Numbers in parentheses show the percentage incidence in each year.
PE, pulmonary embolism.

Table 3 Univariate Analysis of Risk for PE in Autopsy Cases

Year	All PE		Thrombotic PE		Critical PE		Clinacally diagnosed critical PE	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
1987–1990	1.00		1.00		1.00		1.00	
1991–1994	1.08 (1.04–1.13)	0.0004	1.08 (1.03–1.13)	0.001	1.38 (1.28–1.49)	<0.0001	1.16 (0.97–1.40)	0.11
1995–1998	1.16 (1.11–1.22)	<0.0001	1.17 (1.11–1.23)	<0.0001	1.68 (1.56–1.80)	<0.0001	1.40 (1.17–1.67)	0.0003

OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 2.

Results

A total of 11,367 PE cases (2.9%; 5,869 males, 5,474 females, and 24 cases without description of sex) were identified from 396,982 postmortem examinations (249,492 males, 146,484 females, and 1,006 cases without description of sex) between 1987 and 1998[6–17] We excluded cases without confirmation of the diagnosis. There were 4,363 cases of critical PE (2,097 males, 2,258 females, and 8 without description of sex). Cases of thrombotic PE accounted for 91% of all PE (Table 1). The age distribution of cases with all PE had a peak between 60s and 70s for both sexes (Fig 1). The ratio of all PE in autopsy cases by age, however, had a peak in young adults in both sexes (Fig 2). All PE, thrombotic PE, critical PE, and also clinically diagnosed critical PE increased (Tables 2,3). Deep vein thrombosis (DVT) was reported in 1,044 (9.2%) cases among all PE.

As causes of critical PE according to patient age, heart diseases and major operations were prominent from birth to age 9, and almost all of the heart diseases were congenital. In this age group, there were no cases of critical PE diagnosed clinically. Cancer was a risk in many critical PE cases that were older than 10 years. In the 20s and 30s, pregnancy and/or delivery were associated with 38.5% of female cases with critical PE, whereas in males fractures and neuromuscular diseases were involved in 16% and 12.3% of cases, respectively (Table 4).

Both all PE and critical PE occurred at low OR in males, including those under the age of 10 years or older than 39 years (Table 5). In the 20–39 years age group, critical PE was found in 2.3% of autopsy cases. ORs of thrombotic PE were 1.08 (95% CI 1.03–1.13; p=0.001) between 1991 and 1994, and 1.17 (95% CI 1.11–1.23; p<0.0001) between 1995 and 1998, when using the data between 1987 and 1990 as the reference. By similar analysis, ORs of critical PE were 1.16 (95% CI 0.97–1.40; p=0.11) between 1991 and 1994, and 1.40 (95% CI 1.17–1.67; p=0.0003) between 1995 and 1998. Both all PE and critical PE according to Mieno's criteria increased year by year (Table 6).

Critical PE was diagnosed more frequently in the presence of DVT, recent major surgery, and more recent cases. On the other hand, it was less frequent in males and in the presence of cancer, heart diseases, chronic respiratory failure, neuromuscular diseases, and connective tissue diseases (Table 7).

Discussion

PE in Young Adults

Population-based analysis has shown that deaths from PE are increasing in older age groups[1] and the present study results supports this finding. But from the viewpoint of incidence in deaths, PE contributed more to deaths in patients between the ages of 20–39 years than in other age groups. The number of deaths was less in this age group than in older age, but PE was more important as the cause of death. As the cause of natural death in the forensic setting, PE comprised 5.0% of the leading causes of death for ages 18–40; that is, higher than in the 41–60-years age group (<2.7% for ages 41–60, and <2.4% for ages 61–80)[20]

One main reason why the ratio of deaths from PE is higher in the 20–39-years age group compared with other ages is that the overall number of deaths in that cohort is low. Another reason is that there are many cases of PE in females resulting from pregnancy/delivery, which are well-known risk factors for PE. The number of PE reported in the fields of gynecology and obstetrics increased 6.5-fold in 2000 compared with 1991[21] In Japan, the incidence in obstetrics consists of 0.02% of total deliveries, 0.003% of vaginal deliveries, and 0.06% of cesarean deliveries between 1991 and 2000[21] In the United States PE was attributed to 19.8% of maternal deaths between 1974 and 1978, and 23.4% between 1979 and 1986[22,23] In forensic cases, 10 deaths were associated with pregnancy, and 3 of those resulted from PE[24] Of the males in their 20s and 30s, 25% of deaths from PE were associated with a fracture or a neuromuscular disease, which is a higher rate than that in other age groups of males.

PE in Children Aged 0–9

Although pediatric cases of PE are rare, it is suggested that the risk of venous thromboembolism increases when central venous catheters are used[25,26] The present study revealed that fatal PE was not diagnosed clinically in the 0–9 age group and the results indicate that even in children it is necessary to pay proper attention to the occurrence of PE associated with congenital heart diseases or major operations. Autopsy studies in Western countries have shown an incidence of PE ranging between 0.05% and 4.2% in childhood[26] The Canadian Registry of Venous Thromboembolism (VTE) indicated that the incidence of VTE in children (ages 1 month to 18 years) was 5.3/10,000 hospital admis-

Table 4 Characteristics inof Autopsy Cases With Critical PE

Age (years)	*0–9*		*10–19*		*20–39*		*40–59*		*60–70*		*80–*	
Gender	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Critical PE	*30*	*20*	*48*	*14*	*162*	*174*	*517*	*584*	*1,080*	*1,099*	*258*	*367*
Clinically diagnosed critical PE	*0 (0.0%)*	*0 (0.0%)*	*4 (3.4%)*	*2 (3.7%)*	*29 (7.4%)*	*49 (14.0%)*	*84 (5.7%)*	*138 (10.1%)*	*152 (5.0%)*	*225 (8.4%)*	*31 (4.5%)*	*62 (6.7%)*
Cancer	*3 (10.0%)*	*4 (20.0%)*	*25 (52.1%)*	*5 (35.7%)*	*41 (25.3%)*	*47 (27.0%)*	*260 (50.3%)*	*285 (48.8%)*	*585 (54.2%)*	*458 (41.7%)*	*114 (44.2%)*	*112 (30.5%)*
Major operation	*16 (53.3%)*	*10 (50.0%)*	*7 (14.6%)*	*4 (28.6%)*	*39 (24.1)*	*57 (32.8%)*	*133 (25.7%)*	*206 (35.3%)*	*297 (27.5%)*	*303 (27.6%)*	*42 (16.3%)*	*50 (13.6%)*
Heart disease	*19 (63.3%)*	*10 (50.0%)*	*6 (12.5%)*	*2 (14.3%)*	*18 (11.1%)*	*17 (9.8%)*	*58 (11.2%)*	*41 (7.0%)*	*170 (15.7%)*	*148 (13.5%)*	*54 (20.9%)*	*69 (18.8%)*
Neuromuscular disease	*1 (3.3%)*	*1 (5.0%)*	*5 (10.4%)*	*1 (7.1%)*	*20 (12.3%)*	*11 (6.3%)*	*50 (9.7%)*	*46 (7.9%)*	*118 (10.9%)*	*130 (11.8%)*	*26 (10.1%)*	*42 (11.4%)*
Fracture	*0 (0.0%)*	*0 (0.0%)*	*2 (4.2%)*	*2 (14.3%)*	*26 (16.0%)*	*6 (3.4%)*	*20 (3.9%)*	*19 (3.3%)*	*26 (2.4%)*	*49 (4.5%)*	*6 (2.3%)*	*19 (5.2%)*
Pregnancy and/or delivery	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*67 (38.5%)*	*0 (0.0%)*	*8 (1.4%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
*Myocardial infarction**	*1 (5.3%)*	*1 (10.0%)*	*1 (16.7%)*	*0 (0.0%)*	*1 (5.6%)*	*6 (35.3%)*	*36 (62.1%)*	*15 (36.6%)*	*138 (81.2%)*	*100 (67.6%)*	*42 (77.8%)*	*51 (73.9%)*
*Cardiomyopathy**	*0 (0.0%)*	*0 (0.0%)*	*3 (50.0%)*	*0 (0.0%)*	*8 (44.4%)*	*3 (17.6%)*	*10 (17.2%)*	*5 (12.2%)*	*9 (5.3%)*	*9 (6.1%)*	*2 (3.7%)*	*2 (2.9%)*
*Valvular heart disease**	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*2 (11.1%)*	*1 (5.9%)*	*7 (12.1%)*	*7 (17.1%)*	*10 (5.9%)*	*29 (19.6%)*	*4 (7.4%)*	*12 (17.4%)*
*Congenital heart disease**	*18 (94.7%)*	*10 (100.0%)*	*2 (33.3%)*	*2 (100.0%)*	*4 (22.2%)*	*6 (35.3%)*	*2 (3.4%)*	*9 (22.0%)*	*3 (1.8%)*	*5 (3.4%)*	*2 (3.7%)*	*2 (2.9%)*
*Myocarditis**	*0 (0.0%)*	*1 (10.0%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (5.6%)*	*1 (5.9%)*	*0 (0.0%)*	*2 (4.9%)*	*2 (1.2%)*	*2 (1.4%)*	*1 (1.9%)*	*0 (0.0%)*
*Cerebral vascular disease***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*10 (50.0%)*	*6 (54.5%)*	*36 (72.0%)*	*37 (80.4%)*	*96 (81.4%)*	*109 (83.8%)*	*24 (92.3%)*	*39 (92.9%)*
*Brain tumor***	*0 (0.0%)*	*1 (100.0%)*	*0 (0.0%)*	*1 (100.0%)*	*1 (5.0%)*	*1 (9.1%)*	*6 (12.0%)*	*3 (6.5%)*	*6 (5.1%)*	*6 (4.6%)*	*0 (0.0%)*	*2 (4.8%)*
*Degenerative disease***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*2 (18.2%)*	*2 (4.0%)*	*1 (2.2%)*	*10 (8.5%)*	*9 (6.9%)*	*1 (3.8%)*	*2 (4.8%)*
*Traumatic brain injury***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*4 (20.0%)*	*1 (9.1%)*	*3 (6.0%)*	*1 (2.2%)*	*3 (2.5%)*	*4 (3.1%)*	*1 (3.8%)*	*0 (0.0%)*
*Meningitis and/or encephalitis***	*1 (100.0%)*	*0 (0.0%)*	*1 (20.0%)*	*0 (0.0%)*	*1 (5.0%)*	*1 (9.1%)*	*0 (0.0%)*	*1 (2.2%)*	*2 (1.7%)*	*2 (1.5%)*	*0 (0.0%)*	*0 (0.0%)*
*Demyelinating disease***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (2.0%)*	*0 (0.0%)*	*0 (0.0%)*	*2 (1.5%)*	*0 (0.0%)*	*0 (0.0%)*
*Progressive muscular dystrophy***	*0 (0.0%)*	*0 (0.0%)*	*2 (40.0%)*	*0 (0.0%)*	*2 (10.0%)*	*0 (0.0%)*	*2 (4.0%)*	*1 (2.2%)*	*0 (0.0%)*	*1 (0.8%)*	*0 (0.0%)*	*0 (0.0%)*

**Autopsy cases with critical PE and heart disease; **autopsy cases with critical PE and heart disease.*
Abbreviation see in Table 2.

Table 5 Multivariate Analysis of Risk for PE in Autopsy Cases

	All PE		Critical PE	
	OR (95%CI)	p value	OR (95%CI)	p value
Gender				
Female	1.00		1.00	
Male	0.61 (0.59–0.64)	<0.0001	0.53 (0.50–0.56)	<0.0001
Year				
1987–1990	1.00		1.00	
1991–1994	1.10 (1.05–1.14)	<0.0001	1.41 (1.30–1.51)	<0.0001
1995–1998	1.19 (1.14–1.25)	<0.0001	1.73 (1.60–1.86)	<0.0001
Age group				
0–9	0.14 (0.12–0.16)	<0.0001	0.07 (0.05–0.10)	<0.0001
10–19	0.90 (0.76–1.06)	0.22	0.73 (0.56–0.96)	0.02
20–39	1.00		1.00	
40–59	0.67 (0.62–0.73)	<0.0001	0.57 (0.51–0.65)	<0.0001
60–79	0.56 (0.52–0.60)	<0.0001	0.46 (0.41–0.52)	<0.0001
80–	0.51 (0.47–0.55)	<0.0001	0.41 (0.36–0.47)	<0.0001

Abbreviations see in Tables 2,3.

Table 6 Univariate Analysis of Risk for PE Using Mieno's Criteria

Year	Total PE*		Critical PE*	
	OR (95%CI)	p value	OR (95%CI)	p value
1967–1970	0.28 (0.25–0.30)	<0.0001	0.20 (0.16–0.24)	<0.0001
1971–1974	0.51 (0.47–0.54)	<0.0001	0.31 (0.26–0.36)	<0.0001
1975–1978	0.68 (0.64–0.72)	<0.0001	0.46 (0.40–0.52)	<0.0001
1979–1982	0.64 (0.61–0.68)	<0.0001	0.51 (0.46–0.56)	<0.0001
1983–1986	0.86 (0.82–0.91)	<0.0001	0.88 (0.81–0.96)	0.003
1987–1990	1.00		1.00	
1991–1994	1.07 (1.02–1.12)	0.006	1.39 (1.28–1.50)	<0.0001
1995–1998	1.15 (1.09–1.20)	<0.0001	1.68 (1.55–1.81)	<0.0001

**Mieno's criteria (see details in text).*
Abbreviations see in Tables 2,3.

Table 7 Factors Affecting Clinical Diagnosis of Critical PE

	OR (95%CI)	p value
Age (10-year increments)	1.02 (0.98–1.08)	0.35
Male	0.76 (0.64–0.90)	0.002
Deep vein thrombosis	1.40 (1.11–1.77)	0.004
Major operation	1.31 (1.08–1.59)	0.006
Cancer	0.26 (0.21–0.31)	<0.0001
Heart disease	0.36 (0.27–0.48)	<0.0001
Chronic respiratory failure	0.52 (0.42–0.64)	<0.0001
Neuromuscular disease	0.49 (0.37–0.66)	<0.0001
Connective tissue disease	0.18 (0.07–0.46)	0.0003
Fracture	0.70 (0.48–1.02)	0.07
Pregnancy and/or delivery	1.65 (0.97–2.81)	0.07
Coagulopathy	2.46 (0.85–7.09)	0.09
Year (10-year increments)	1.72 (1.35–2.18)	<0.0001

OR less than 1.00 means more difficult to diagnose clinically.
Abbreviations see in Tables 2,3.

sions or 0.07/10,000 children.[27] Thereafter, the Canadian Childhood Thrombophilia Registry showed that 2.2% of children with VTE that was directly associated with deaths, and was central venous line-associated thrombosis.[28]

Incidence of PE

The present study showed that deaths from PE confirmed in autopsy have slightly but significantly increased in Japan, which is consistent with the results from death certificates[1] and in clinical settings.[29–31] Improvement in diagnostic techniques, incremental increase of the geriatric population, and westernization of life style are suggested as factors causing the increase of PE in Japan.[29–31]

The changes in the incidence of autopsy-proven PE by year differ among countries. An autopsy study from Hong Kong documented a rising trend of PE from 1975 to 1989.[32,33] Conversely, the incidence of PE in autopsies reduced in the United States from 1966 to 1980,[34] and in the United Kingdom from 1965 to 2000,[35,36] but a Swedish study indicated that the incidence of PE was unchanged from 1957 to 1987.[37] These differences may be related to differences in clinically diagnostic accuracy, in population structure, in prophylaxis and management of DVT/PE, and in life style.

Rate of Diagnosis of PE

We indicate that the incidence of clinically diagnosed critical PE is increasing, but it was only 22% in 1998. Walden et al showed that, in 425 autopsy cases with PE, 14% was diagnosed before death, 30% was written first on the death certificate, and 56% was revealed in autopsy.[4] Another report indicated that, in 92 cases confirmed as PE by autopsy, 49% was considered as PE before autopsy and the remaining 51% was diagnosed by autopsy. Moreover, PE was assigned as the cause of death on the death certificate or in the medical report in 32% of 92 cases.[5] In recent reports, only approximately 20% of PE confirmed by autopsy was diagnosed clinically.[38,39] On the other hand, there was improvement in the diagnosis of PE in a Swedish study.[40] Taken together, all the results shown indicate that fatal PE is difficult to diagnose before death.

PE was diagnosed before death more accurately in the presence of DVT, recent major operation, and more recent cases, but was difficult to diagnose in association with collagen diseases, cancer, heart diseases, neuromuscular diseases, chronic respiratory failure, and in males. This finding partly confirms the finding that diagnosis of PE delayed in clinical cases, as we previously reported, when cardiac disease or pulmonary diseases exist.[1]

Study Limitations

We could not sufficiently analyze the incidence of DVT in cases with PE. Generally, DVT is found in many cases of PE. DVT was detected in 165 legs (95%) among 174 legs from 87 autopsy cases with PE in a medical examiner's office.[1,2] Clinically, DVT was found in 84.6% and 87.5% of cases of acute PE on the day it was diagnosed or the next day, respectively.[4] However, in the present study, DVT was found in only 9.2% of cases with PE. The discrepancy between the previous reports and the present study may be related to insufficient examination for DVT in routine autopsy.

Conclusion

Compared with other ages, PE contributed more to deaths in those aged 20–39 years. In recent years, deaths from PE have been slightly but significantly increasing in Japan. The incidence of clinically diagnosed critical PE has also been increasing.

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The Günther-Tulip Retrievable IVC Filter

— Clinical Experience in 118 Consecutive Patients —

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Background The purpose of this study was to assess the use of the Günther Tulip Filter (GTF) for the management of venous thromboembolism (VTE).

Methods and Results Between December 2000 and April 2005, 118 patients (42 males, 76 females; mean age 60.5 years) diagnosed with VTE, underwent treatment with a GTF. The filter was left permanently in 52 patients. In the other 66 patients, attempts were made to retrieve it, with success in 60 cases (90.9%). No major complication was found throughout the filter's use. Of the 58 patients with the permanent filters, 41 underwent enhanced computed tomography at follow-up in the chronic phase. Thirty-eight filters (92.7%) remained patent, and under low-intensity anticoagulation therapy (international normalized ratio 1.8±0.4), the patency rate was 97.1%. Penetration of the inferior vena cava (IVC) wall by the filter's struts beyond a distance of 3 mm occurred in 23 patients (56.1%), but there was no observable leakage from the IVC or injury to adjacent organs.

Conclusions The GTF is feasible and safe for treating VTE. When used permanently, GTFs have a high patency rate, and there is neither leakage from the IVC nor injury to adjacent organs in the event of penetration by the struts. (*Circ J* 2008; **72:** 287–292)

Key Words: IVC filter; Prevention; Pulmonary thromboembolism

Pulmonary thromboembolism is usually caused by a thrombus formed within the veins of the lower extremities or pelvis. It is a serious circulatory disorder, which may cause sudden death if the blockage affects an extensive area of the pulmonary vascular bed. The use of an inferior vena cava (IVC) filter has proved effective in preventing the thrombus from flowing into the pulmonary circulation[1–7] However, it has been reported that the preventive effect of the IVC filter is evident in the acute phase of venous thromboembolism (VTE), but in the chronic phase, there is a significant increase in the rate at which thrombi occur in the filter and of recurrence of deep vein thrombosis (DVT) in the lower extremities[8] It is therefore considered preferable to use a non-permanent type of IVC filter in the short, acute period of the disease, during which time the patient is at greater risk of developing thromboembolism. An IVC filter for temporary implantation has recently been developed[9] and it has to be removed within 2 weeks of implantation because it is directly connected to the catheter; however, its extraction can be difficult if a large thromboembolus is trapped within the filter. There are also risks of infection and hemorrhage at the implantation site, as well as the necessity for bed rest if the filter is introduced through the femoral vein[10,11] The retrievable IVC filter used in the present study (Günther Tulip Vena Cava MReye Filter; William Cook Europe, Bjaeverskov, Denmark: herein referred to as Günther Tulip Filter (GTF)) can be used as a permanent type or can be retrieved as required after implantation[12,13]

This retrospective study evaluated the feasibility, effectiveness, and complications associated with the use of a retrievable IVC filter for the prevention of pulmonary thromboembolism in patients with acute DVT. In addition, we evaluated the patency rate in the chronic phase beyond 3 months after implantation and the incidence with which struts penetrate the IVC wall in patients with permanent GTFs.

Methods

During a period of 52 months (December 2000 to April 2005), 118 patients (42 males, 76 females), aged 18–86 years (mean 60.5±14.8), underwent implantation of a GTF at Mie University Hospital.

All patients underwent imaging, including venous ultrasonography, venography and/or pelvic-abdominal enhanced computed tomography (CT), to document DVT, except for patients with severe pulmonary thromboembolism and circulatory disorders where there was no time to adequately evaluate the existence of DVT.

Indications for placement were based on the institutional protocol, according to studies already reported[14,15] and the Japanese guideline[16] and included: (a) proximal DVT involving the popliteal vein, especially with a free-floating thrombus; (b) massive pulmonary thromboembolism with no time to adequately evaluate the existence of proximal DVT; (c) proximal DVT treated using thrombolytic therapy with or without a catheter; and/or DVT with (d) poor cardiopulmonary function and (e) contraindications to anticoagulation therapy.

At the time of implantation, we used the GTF as a per-

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Table 1 Patient Characteristics

	n (M/F)
Underlying disease	
Malignancy	39 (12/27)
Genitourinary	15 (2/13)
Gastrointestinal	12 (9/3)
Gynecologic	5 (0/5)
Lung	2 (0/2)
Central nervous system	2 (0/2)
Breast	1 (0/1)
Sarcoma	1 (1/0)
Lymphoma	1 (0/1)
Orthopedic disease	20 (5/15)
Central nervous system disorder	10 (5/5)
Pelvic mass (excluding malignancy)	5 (1/4)
Infection	5 (3/2)
Inflammatory bowel disease	3 (2/1)
Multiple trauma	2 (1/1)
Pregnancy	2 (0/2)
Gastrointestinal disease (excluding malignancy)	2 (2/0)
Renal disease	2 (1/1)
Collagen disease	1 (0/1)
None	27 (11/16)
Other risk factor for venous thromboembolism (including overlap)	
Immobilization	47 (19/28)
Postoperative status	43 (14/29)
Obesity	28 (6/22)
Indwelling catheter	7 (6/1)
Estrogen-replacement therapy	5 (1/4)
Thrombophilia	4 (3/1)
Protein C deficiency	1 (1/0)
Protein S deficiency	3 (2/1)

manent filter for VTE patients with not only a proximal, free-floating thrombus but also contraindications to anticoagulation therapy or poor life expectancy with malignant disease or age over 80 years. For the other patients, we initially planned to retrieve the filter.

In deploying the GTF we followed the Japanese guideline[16] for use of IVC filters, in which there are no contraindications to the temporary use, but some contraindications to permanent use: (a) occluded IVC; (b) no access to IVC; and (c) pregnancy.

All patients gave written informed consent prior to the implantation.

Implantation

To implant the filter, its sheath was inserted into the right internal jugular or right femoral vein. Inferior vena cavography was performed using the Berman angio-balloon catheter (ARROW, Reading, PA, USA) to identify the section where the renal vein and vena cava merge. A guidewire was used to advance the catheter plus filter (outside diameter 10F) slightly beyond the final position, then the sheath was slowly removed and the filter legs extended. When the filter was appropriately positioned, the end-hook was released to complete the implantation. If there was a problem with the location, the filter was retracted into the sheath before releasing the hook, and the placement process was repeated.

Treatments During Implantation

Intensive anticoagulation with an intravenous bolus of unfractionated heparin, followed by continuous infusion, was performed with no interruption during the implantation process in all the patients without contraindications. The dose of unfractionated heparin was adjusted to maintain the activated partial thromboplastin time at 2–2.5-fold the control value.

Warfarin was administered after thrombolysis. For patients not treated with thrombolysis, warfarin was administered within a few days of beginning anticoagulation with unfractionated heparin. The dose of warfarin was adjusted to maintain the international normalized ratio (INR) of prothrombin time at approximately 2.0. Heparin infusion was discontinued after a therapeutic range of INR (1.5–2.5) was obtained for at least 2 consecutive days. The duration of anticoagulation was basically defined according to the Japanese guideline[16] Unless there were contraindications to anticoagulation therapy, the patients with the GTF as a permanent filter received warfarin indefinitely, according to expert opinion[17,18]

Pharmacological and/or pharmacomechanical thrombolysis was used in (a) patients without contraindications of the treatment; (b) patients with pulmonary thromboembolism accompanied by shock or persistent hypotension; (c) patients with right ventricular dysfunction detected on echocardiography, despite stable hemodynamics; and (d) patients with DVT in the iliofemoral vein or IVC. Written consent was given by the patients before treatment. In principle, 240,000 units of urokinase, the only thrombolytic able to be used for the treatment of VTE in Japan at the time this study started, were administered systemically or catheter-directly, 3 times per day[19] Ascending venography, venous ultrasonography, or enhanced CT was used every 1–3 days for observation, which enabled the treatment to be suspended until reduction or elimination of the DVT occurred.

Filter Retrieval

The filter was retrieved when the venous thrombus was eliminated after treatment, or when only residual mural thrombus was detected after 1 week or more of treatment with pharmacological and/or pharmacomechanical thrombolysis. Before attempting to retrieve the filter, cavography or enhanced CT was performed to detect thrombus trapped within the filter. The filter was retrieved when the thrombus measured 1×2 cm or smaller, or was not detected at all. If that size thrombus or larger was trapped, further treatment with systemic pharmacological thrombolysis was performed before attempting filter retrieval[20]

For retrieval, a guidewire was advanced to beneath the filter. The puncture site was extended using the dilator, and then the sheath system (introducer, retrieval catheter, sheath, maximum outer diameter 13F) was advanced close to the filter. The introducer was extracted and the loop-wire catheter inserted. The loop-wire was fully extended and the hook snared at the filter tip. The sheath was advanced without pushing the filter out of position and the loop-wire pulled lightly to fix the hook. Care was taken to avoid damaging the IVC wall with the filter anchor. The sheath was then advanced without moving the filter itself, the filter reloaded in the retrieval catheter, and the catheter removed. Just after retrieval, the IVC wall was checked by cavography for any damage or perforation.

Points for Evaluation

The entire implantation and retrieval process was evaluated for the following: indications; implantation approach site; location and period of implantation; technical feasibility of filter placement and retrieval; retrieval time and success rate; reasons for deciding against retrieval; occurrence of symptomatic pulmonary thromboembolism after im-

plantation and during/after retrieval of the filter; and rate of complications such as hemorrhage, infection, vascular damage, air embolus, tilting, asymmetrical dilation, displacement, misinsertion, and filter fracture. All patients from whom the GTF was not retrieved because of a huge residual thrombus in the IVC (below the filter), pelvic region, and/or proximal lower extremity received anticoagulant therapy without contraindications. In the chronic phase, we used enhanced CT to evaluate whether or not the filters left permanently were occluded with thrombus. Furthermore, we evaluated whether the struts of the filters penetrates the IVC wall by more than 1 mm.

Results

Patient characteristics are shown in Table 1. The total dose of urokinase used for the treatment of DVT was 3,100,000±1,900,000 units in 6.1±3.4 days.

As for the method of implantation, 116 filters were implanted using the right internal jugular vein approach and only 2 were implanted using the right femoral vein approach. There were no complications with the implantations. The filters were implanted in the IVC below the renal vein inflow, except in 13 patients with IVC thrombosis extending to the proximal portion of the renal vein inflow (n=7), with IVC stenosis below the renal vein inflow (n=5), or with duplicated IVC (n=1). For these patients, the filter was implanted in the IVC above the renal vein inflow. There was no misplacement, such as implantation in an iliac vein or other branch of the IVC, and no occurrence of major hemorrhage (decrease in hemoglobin level ≥2 g/dl or requirement for a blood transfusion), asymmetric dilation, tilting (≥20°) on post-implantation frontal and lateral views of the cavogram, displacement, damage to the IVC wall, fracture of the filter, infection, or air embolus associated with the procedure.

The purpose of the implantation is listed in Table 2. Filters were not retrieved in 58 patients for the reasons listed in Table 3. The filter was initially implanted permanently in patients because of age over 80 years (n=3), poor prognosis of other preexisting disease (n=21), and/or contraindication to anticoagulation therapy (n=13). In 21 patients GTFs were not retrieved, although retrieval had been planned initially, because of residual thrombus with the possibility of disengagement, such as the free-floating type, after treatment (n=15) and failure to retrieve (n=6). Attempts at retrieval were made in 66 patients, with 60 successful attempts. Consequently, the success rate of retrieval was 90.9%. In these patients, post-retrieval venography detected no damage to the IVC wall and no leakage of contrast media outside the blood vessels. During the retrieval process, 2 filters were dropped in the IVC, but were successfully retrieved with a retrieval kit. The mean duration of filter implantation was 10.1±6.2 days (2–37 days), and the average actual time to remove the filter was 6.1±5.4 min (2–40 min). No clinically evident pulmonary thromboembolism occurred during implantation or retrieval of the filters.

The longest interval from implantation to retrieval was 37 days. In that case, after the thrombus was successfully lysed

Table 2 Reasons for Using an IVC Filter

	n (%)
Proximal DVT including popliteal vein	*111 (94.0)*
Prevention of APTE during thrombolytic therapy	*71 (60.1)*
Prevention of recurrent APTE	*59 (50.0)*
DVT (+)	*54 (45.7)*
DVT (unknown)	*5 (4.2)*
Proximal DVT under treatment with catheter-directed thrombolysis	*55 (46.6)*
Free-floating thrombus	*27 (22.8)*
Poor cardiopulmonary function	*22 (18.6)*
Contraindications to anticoagulation therapy	*9 (7.6)*
Prevention of APTE at delivery/operation	*5 (4.2)*
Recurrence of VTE under well-controlled anticoagulation therapy	*4 (3.3)*

IVC, inferior vena cava; DVT, deep vein thrombosis; APTE, acute pulmonary thromboembolism; VTE, venous thromboembolism.

Table 3 Reasons for Not Removing IVC Filter

	n (%)
Poor prognosis of other preexisting disease	*21 (36.2)*
Residual thrombus with possibility of disengagement	*15 (25.9)*
Contraindication to anticoagulation therapy	*13 (22.4)*
Failure to retrieve	*6 (10.3)*
Age >80 years	*3 (5.2)*

Abbreviation see in Table 2.

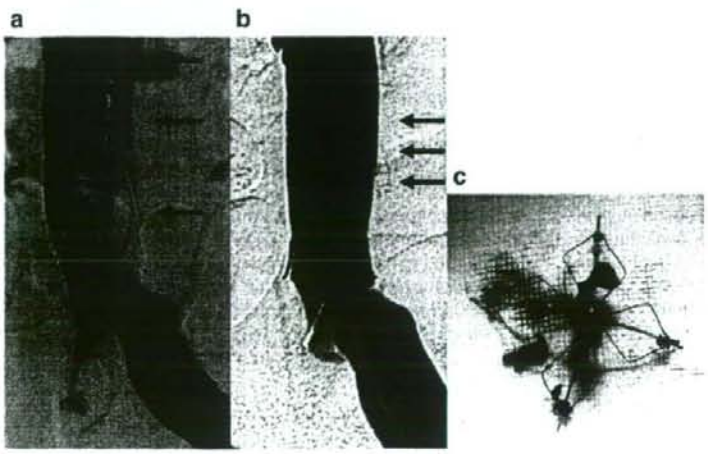

Fig 1. Images from a 42-year-old woman with lower extremity deep vein thrombosis after treatment of a tibial bone fracture, in whom the Günther Tulip Filter (GTF) trapped a large thrombus following thrombolytic therapy with the catheter. (a) Inferior vena cavogram shows the presence of the thrombus inside the filter. (b) Additional pharmacological thrombolysis reduces the size of the thrombus and retrieval is successful without the occurrence of pulmonary thromboembolism. (c) Removed GTF with a small, residual thrombus.

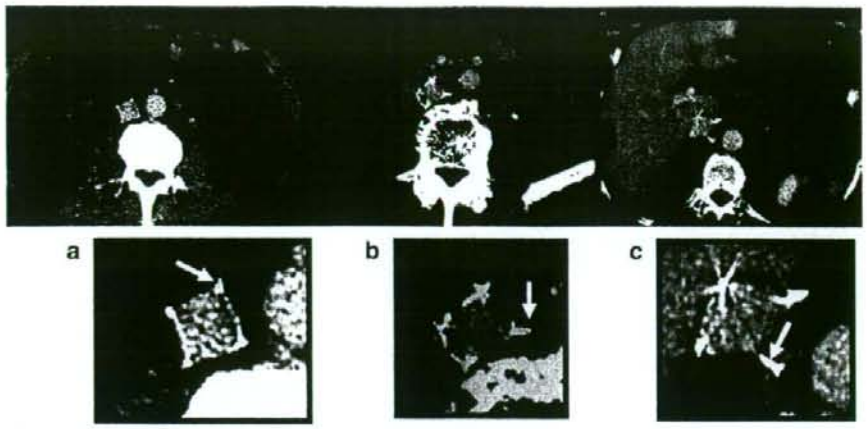

Fig 2. Extent of penetration of filter struts in 41 patients implanted with Günther Tulip Filter as a permanent filter who underwent enhanced computed tomography. (a) Penetration of the inferior vena cava (IVC) wall less than 3 mm (n=18; 43.9%). (b) Penetration of the IVC wall from 3 mm to 6 mm (n=20; 48.8%). (c) Penetration of the IVC wall more than 6 mm (n=3; 7.3%).

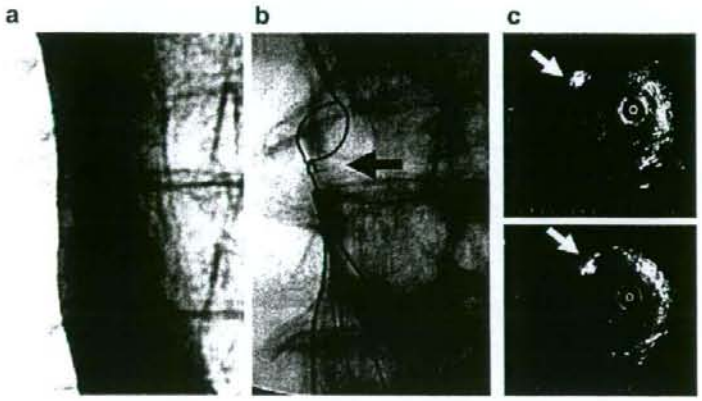

Fig 3. Images from a 78-year-old man with documented massive pulmonary thromboembolism and lower extremity deep vein thrombosis who underwent successful insertion of a Günther Tulip Filter (GTF) and thrombolytic therapy. After the thrombus disappeared, removal of the GTF failed. (a) Vena cavogram shows the hook of the GTF attached to the vein wall at 10°. (b) The loop-wire can not snare the hook. (c) The intravenous ultrasound image shows the GTF hook attached to the inferior vena cava wall, and a high-intensity echogram shows supposed fibrin deposits around the hook.

with catheter-directed pharmacomechanical thrombolysis, a fraction of the thrombus was released and trapped within the filter. Additional systemic thrombolysis eliminated the trapped thrombus and the filter was retrieved. The retrieval procedure was easy, although the filter's struts were adhered lightly to the IVC wall. After retrieval, cavography and enhanced CT revealed no extravascular leakage or intraperitoneal hemorrhage.

Among the 60 filters retrieved, inferior vena cavograms revealed 5 large thrombi trapped within (Fig 1) and in all 5 cases, the filters were successfully retrieved after additional pharmacological and/or pharmacomechanical thrombolysis eliminated the thrombus. Of the 58 patients with a permanent filter, 41 underwent follow-up CT for screening of thrombi around the filter more than 3 months post implantation (3–39 months, average 11.7 months). The other 17 patients were not followed up because of: death unrelated to pulmonary thromboembolism (n=11, cancer: 9, bleeding: 2), renal dysfunction (n=2), distance from hospital (n=1), or inadvertent oversight (n=3). Among the 41 patients followed up, 38 had filters that remained patent, making a patency rate of 92.7%. Of the 3 patients with occluded filters, 2 of them had the occlusion confirmed by CT at 9 and 36 months after implantation and did not receive anticoagulation therapy because of preexisting intracerebral bleeding (n=1) and cessation of follow-up (n=1). The third patient had an ovarian mucinous adenocarcinoma. Of the 41 patients, 35 received anticoagulation therapy (average INR 1.84±0.42), under which the filter patency rate was 97.1% (34/35). Only 1 patient, a 51-year-old man, developed a pulmonary thromboembolism during the mean observational period of 12.5±12.1 (1–40) months after implantation for permanent use. He also had contraindications to anticoagulation therapy because of cerebral hemorrhage. Three weeks after implantation, symptomatic pulmonary thromboembolism occurred, even though during that period he did not have symptoms suggestive of DVT.

We used enhanced CT to also assess the extent and frequency of penetration by filter struts. Penetration greater than 3 mm occurred in 23 patients, and more than 6 mm in 3 patients. However, neither leakage from the IVC nor injury to adjacent organs was observed (Fig 2).

Discussion

Conventionally, surgical intervention, such as IVC liga-

tion or plication, is used to prevent pulmonary thromboembolism caused by DVT,[1,22] although percutaneous implantable filters for the IVC have also proven effective.[2–7]

According to a review of the use of permanent IVC filters by Becker et al,[8] recurrent clinical pulmonary embolism is rare after filter placement. Complications are common, but rarely life threatening, and among the reviewed studies only 0.16% of deaths were from complications. However, although permanent filters are effective in preventing acute pulmonary thromboembolism, it has been demonstrated that they significantly increase the rate of recurrence of DVT in the follow-up period.[8,23]

Therefore, it has been suggested that non-permanent filters be implanted for the acute period only, during which the risk of the thrombus disengaging is high. In Japan today there are 2 types of non-permanent filters: temporary and retrievable.[24]

The temporary filter is useful because of the certainty that it can be removed, but there can be problems such as thrombosis (16%) and dislocation (4.8%).[9] The Japanese Society of Pulmonary Embolism Registry has reported that among 194 patients in Japan who received temporary filters, 10 patients developed filter-related infections (5.2%) and 3 filters were displaced (1.6%).[11]

The retrievable filters used in the present study can be used permanently or temporarily. They can be implanted during the acute period of DVT when the thrombus is likely to disengage, and retrieved when no longer necessary after reduction or lysis of the thrombus.[25–27]

In the present study the rate of recurrence of pulmonary thromboembolism did not differ between the GTF and other permanent filters, and there were no major complications around the site of insertion.

The GTF has advantages over the temporary type because it can be left in permanently if retrieval is difficult (ie, when a thromboembolus is trapped within the filter or pharmacological and/or pharmacomechanical thrombolysis fails to eliminate the thrombus and there is a risk of disengagement, such as with the free-floating type).[28] Furthermore, there were no cases of infection or filter displacement, and it has been reported that these risks are lower with retrievable IVC filters than with temporary filters,[11,29–31] probably because retrievable filters are not exposed outside the patient's body.

With regard to thrombi trapped in retrievable filters, Millward argues that although they may cause thromboembolism, a thrombus of 1×2 cm or less has minimal impact in patients with preserved cardiopulmonary function, and can be retrieved together with the filter.[20] In the present study, 5 patients had thromboemboli larger than that trapped in the filter, but additional pharmacological thrombolysis caused lysis and retrieval of the filter was successful.

The GTF proved to have considerable advantages over the conventional filters and is considered most appropriate for DVT with transient risk. However, although the GTF is useful for the treatment of DVT, it can be difficult to retrieve. In a previous study, 1 of 11 filters implanted in dogs was irretrievable by 2 weeks after implantation because they were firmly adhered to the vessel wall.[32] The venographic profile of the irretrievable filters in the present study also indicated that the hook of the filter was attached to the vein wall. Among 6 cases of retrieval failure, 2 patients were imaged by intravascular ultrasound to reveal the reason for the unsuccessful retrieval and in each case the filter's hook was found to be attached to the IVC wall and high-intensity echograms revealed fibrin deposits around the hook (Fig 3). We therefore considered that turbulent flow had probably occurred around the hook attached to the IVC wall, inducing the deposition of fibrin, and both the adhesion of the hook to the IVC wall and the fibrin deposits interfered with efforts to snare the hook with the retrieval kit. Therefore, if an IVC filter is to be retrieved, care should be taken to avoid contact between the hook and the vascular wall and where possible, to keep the hook afloat with its open side facing the lumen. When using the right internal jugular vein approach, it is preferable to check the angle of the hook from 2 directions before its release, and repeat the implantation process if necessary.

A conclusion has not been reached as to the duration of implantation before retrieval, but the experiment in dogs indicates that firm adhesion starts between the filter and the vascular wall after 2–3 weeks. However, some researchers argue that adhesion occurs at a slower rate with anticoagulant therapy,[33] suggesting that intensive treatment with an anticoagulant may allow for an implantation period of up to 1 month. The longest period from implantation to retrieval reported to date is 317 days.[34]

In the present study, there was no recurrence of symptomatic DVT in the patients with permanent implantation of a GTF. The PREPIC study found that symptomatic DVT occurred in 36% of patients with a permanent filter at 8-year follow-up[33] but in that study, only 35% of patients were on anticoagulation therapy. In our study, 85% of patients with a permanent GTF received anticoagulation therapy, which is 1 of the reasons why there was no recurrence of symptomatic DVT.

We also evaluated the risk of IVC thrombus around the GTF in the chronic phase, because there are no previous reports of this. In this study, 33% of patients without anticoagulation therapy had total occlusion, whereas the patency rate of the filters was much higher in the patients on anticoagulant therapy (97%), which suggests that anticoagulation therapy after permanent implantation should be continued for the prevention of DVT recurrence and occlusion of the filter in the chronic phase.

We found that the filter struts had penetrated the IVC wall more than 3 mm in 23 patients; moreover, 3 filters had penetrated more than 6 mm. There was no leakage around the IVC, even in those patients under anticoagulation therapy (Fig 2). The strut penetration did not induce complications such as retroperitoneal hemorrhage, surrounding organ damage, etc. However, penetration always carries a risk of complications, so improvement of the design of the struts is needed.

Although the GTF is useful for the management of DVT, its indications are still unclear. At present, the GTF is classified as retrievable, but evidence for the use of this type of filter is limited and the Japanese guideline[16] does not mention its usage. Therefore, use of this filter should be based on that of the temporary type and, in this instance, on the indications for a filter classified as class IIb according to the Japanese guideline.[16] However, retrieval-type filters may overcome the weakness of temporary filters and the indications may be extended with the accumulation of more data.

Conclusions

(1) The retrievable IVC filter used in this study was as effective as the conventional type for prevention of pulmonary thromboembolism caused by DVT in the lower

extremities, pelvis, or IVC. (2) Complications seldom occurred, and the risks of infection and filter displacement were lower than with the use of the temporary filters. (3) Retrieval is simple, but care should be taken to avoid contact between the hook of the filter tip and the IVC wall when implanting. (4) Preference for the retrievable filter is expected to spread because of the fact that it can be implanted permanently but also retrieved when no longer necessary (eg, when the thrombus is lysed). (5) When used permanently, GTFs have a high patency rate and are effective in preventing pulmonary thromboembolism under low-intensity anticoagulation therapy.

A large follow-up study is necessary to examine the performance of the retrievable filter for permanent use, focusing on its preventive effect against pulmonary thromboembolism, prognosis, and occurrence of complications at a later date.

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Pulmonary Thromboembolism in Obstetrics and Gynecology Increased by 6.5-Fold Over the Past Decade in Japan

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Background Although pulmonary thromboembolism (PTE) has been considered relatively uncommon in Japan, its incidence has been on the increase in recent years.

Methods and Results To verify the incidence of PTE in Japan, PTE cases of obstetrics and gynecology were investigated among 102 facilities throughout Japan between 1991 and 2000. A total of 254 cases were enrolled, showing a 6.5-fold increase over the past 10 years. PTE occurred in 0.02% of total births; 0.003% after vaginal deliveries and 0.06% after cesarean births (C/S), of which 14.5% resulting in fatality. The mortality rate was 2.5 per 100,000 deliveries. The incidences among gynecological cases were 0.08% of total operations; 0.03% in benign diseases and 0.42% in malignant diseases of which 13.5% resulting in fatality. The mortality rate was 10.8 per 100,000 operations. The risk was 22 times higher in C/S compared with vaginal deliveries, 16 times higher in malignant diseases compared with benign diseases.

Conclusions As our present survey has shown, PTE has been on the rise in Japan in recent years. C/S and malignant diseases are strong risk factors in obstetrics and gynecology. (*Circ J* 2008; **72:** 753–756)

Key Words: Cesarean births; Malignant diseases; Ovarian cancer; Pulmonary thromboembolism

Pulmonary thromboembolism (PTE) is an extremely serious condition with a mortality rate of 18–30% if left untreated. It has long been the leading cause of maternal mortalities in the West[1–4] although considered to be uncommon in Japan. However, the incidence of PTE has been increasing in recent years as Japanese eating habits have become more similar to the West. In a 1999 patient survey, the Ministry of Health, Labor and Welfare in Japan reported 4,000 patients with PTE and 1,738 deaths from PTE, representing a 3-fold increase per decade[5] The annual age-adjusted PTE mortality rates markedly increased in both sexes in every decade. Finally in the 1980s, women exceeded men in age-adjusted deaths and mortality rates[5] According to the analysis of 309 cases of acute PTE by the Japanese Society of Pulmonary Embolism Research, the main risk factors were considered to be recent major surgery, cancer, prolonged immobilization, and obesity[6] Among 110 cases of recent major surgery, PTE occurred in association with orthopedic surgery (29.1%), general surgery (21.8%), gynecological surgery (18.2%), and others. Moreover, in-hospital mortality rate was 14%. Furthermore, according to maternal and child health statistics in Japan, the maternal mortality rate attributed to obstetrical PTE was 23.5% in 1995 and 22.4% in 2001, making PTE the leading cause of direct obstetrical deaths[7] However, no extensive surveillances of PTE in the field of obstetrics and gynecology have been conducted in Japan.

In the present study we have investigated the incidence of PTE in obstetrics and gynecology in Japan to verify the recent status of PTE.

Methods

The Japan Society of Obstetrics, Gynecological and Neonatal Hematology surveyed 105 university hospitals and 80 general hospitals throughout Japan from 1991 to 2000 to verify the recent status of PTE. Questionnaires concerning numbers of delivery, operation, and PTE cases were sent to all hospitals. PTE was definitely diagnosed by clinical signs and imaging studies, such as computed tomography, pulmonary angiography or pulmonary scintigraphy. In PTE cases, furthermore, date of onset, age, body mass index (BMI), time of onset, background, complications and prognosis were inquired. Ethical approval for the research was obtained from the Ethics Committee of each institution. Odd ratios (OR) with corresponding 95% confidence intervals (CI) were estimated by univariate analysis, and p values were calculated by chi-square statistics, with $p<0.05$ considered as statistically significant. Obstetrical and gynecological cases without thromboembolism provided by Aiiku Hospital, Sapporo Medical Center and Toyama University Hospital were used as control data.

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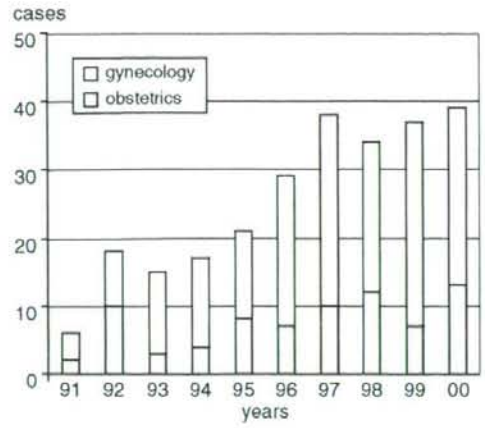

Fig 1. Number of pulmonary thromboembolism cases in obstetrical and gynecological patients.

Results

Registration of clinically diagnosed PTE was completed in 68 university hospitals and 34 general hospitals (recovery rate: 55.1%). Seventy-six obstetrical cases and 178 gynecological cases have been reported between 1991 and 2000 among the 102 facilities, showing a significant increase over time (Fig 1). PTE occurred in 0.02% of total births (76/436,084); 0.003% (9/348,702) after vaginal deliveries and 0.06% (50/87,382) after cesarean births (C/S), of which 14.5% (11/76) resulting in fatality (Table 1). The mortality rate was 2.5 per 100,000 deliveries. The risk of PTE was 22 times higher in C/S compared with vaginal deliveries. The incidences among gynecological cases were 0.08% of total operations (178/221,505); 0.03% (50/191,286) in benign diseases and 0.42% (128/30,219) in malignant diseases of which 13.5% (24/178) resulting in fatality (Table 1). The mortality rate was 10.8 per 100,000 operations. The risk of PTE was 16 times higher in malignant diseases compared with benign diseases.

Fig 2 shows the different onset periods of obstetrical PTE cases. Seventeen cases (22.1%) developed PTE prepartum (6–38 weeks), whereas 59 cases (77.9%) had onset postpartum. Fifty cases among 59 cases (84.7%) developed PTE after C/S. The onset period appeared as 3 peaks: early pregnancy, midterm to late pregnancy, and postpartum. Early pregnancy onset was observed from the 6th gestational week and reaching the first peak between 8 and 11 weeks. PTE recurs after 27 weeks forming a second peak, in midterm to late pregnancy. The final largest peak was observed postpartum, with the highest incidence on day 1. A total of 92%

Table 1 Incidence of Pulmonary Thromboembolism Cases

Obstetrical patients	*76*
Prepartum onset	*17*
Postpartum onset	*59*
Per total deliveries	*0.02% (76/436,084)*
Per vaginal deliveries	*0.003% (9/348,702)*
Per cesarean sections	*0.06% (50/87,382)*
Mortality rates	*14.5% (11/76)*
Gynecological patients	*178*
Benign diseases	*50*
Malignant diseases	*128*
Per total operations	*0.08% (178/221,505)*
Per benign diseases	*0.03% (50/191,286)*
Per malignant diseases	*0.42% (128/30,219)*
Mortality rates	*13.5% (24/178)*
Benign diseases	*10.0% (5/50)*
Malignant diseases	*14.8% (19/128)*

Analysis of personal data among 254 pulmonary thromboembolism cases.

Table 2 Univariate Analysis of Pulmonary Thromboembolism Cases

	OR (95%CI)	*p value (chi-square)*
Obstetrical patients		
BMI >25	*1.89 (1.01–3.55)*	*<0.05*
BMI >27	*3.47 (1.75–6.91)*	*<0.001*
Cesarean section	*14.27 (6.89–29.55)*	*<0.0001*
Gynecological patients benign diseases		
BMI >25	*4.80 (2.20–10.40)*	*<0.001*
Malignant diseases		
BMI >25	*2.40 (1.40–4.20)*	*<0.01*

OR, odds ratio; CI, confidence interval; BMI, body mass index.

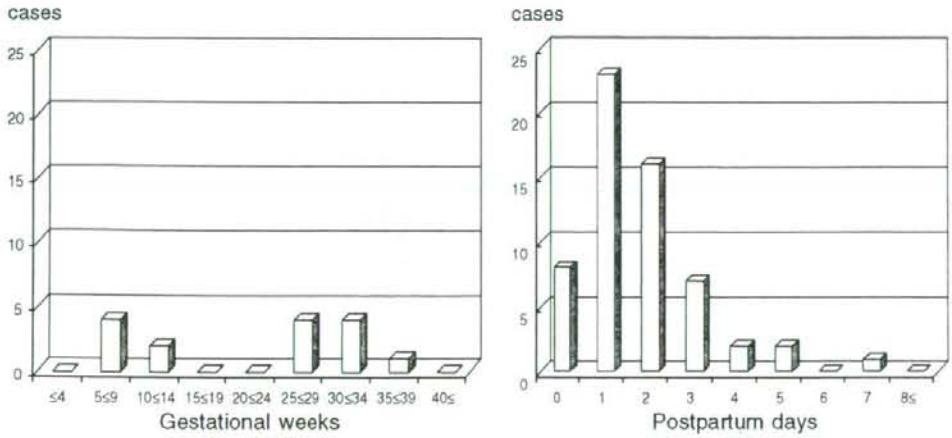

Fig 2. Number of pulmonary thromboembolism cases in obstetrical patients by gestational weeks and postpartum days.

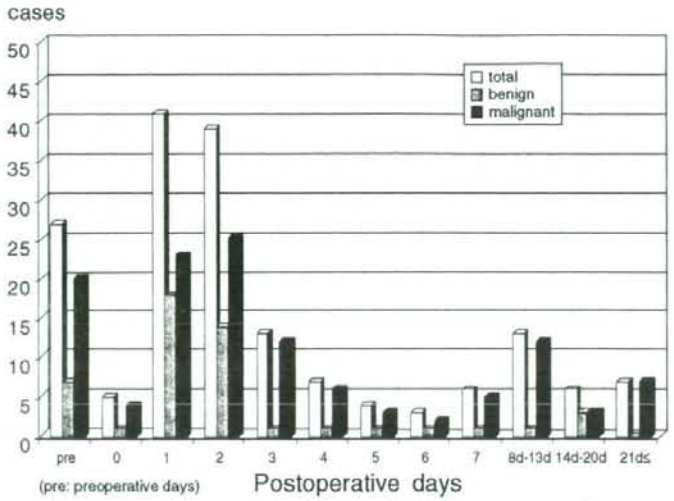

Fig 3. Number of pulmonary thromboembolism cases in gynecological patients by perioperative days.

of postpartum PTE occurred within 3 days postpartum, and all occurred within the first week. Univariate analysis showed that PTE onset was associated with BMI >25 (kg/m^2) (OR 1.89; 95% CI 1.01–3.55; p<0.05), >27 (OR 3.47; 95% CI 1.75–6.91; p<0.001), as well as C/S (OR 14.27; 95% CI 6.89–29.55; p<0.0001) (Table 2).

In gynecological PTE patients, 27 cases (15.2%) showed preoperative onsets: 7 cases (25.9%) in benign diseases and 20 cases (74.1%) in malignant diseases. Among malignant diseases, 15 cases (75%) had ovarian cancer. Postoperatively, PTE shows a large peak on day 1 and 2 (80 cases, 55.6%) and subsequently declines, although some cases were registered as late as 3 weeks postoperatively (Fig 3). PTE was reported among endometrial cancer (53 cases) and ovarian cancer (47 cases) (Fig 4). Univariate analysis showed that the onset of PTE was associated with BMI >25 in both benign (OR 4.8; 95% CI 2.2–10.4; p<0.001) and in malignant diseases (OR 2.4; 95% CI 1.4–4.2; p<0.01) (Table 2).

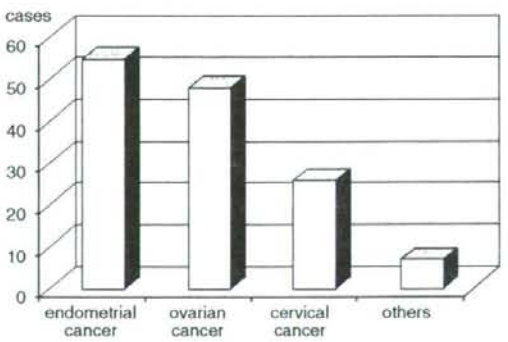

Fig 4. Number of pulmonary thromboembolism cases by malignant diseases.

Discussion

Venous thromboembolism (VTE), which had been considered a relatively rare disease in Japan, has been on the increase in recent years possibly as eating habits have become more similar to those of the West. Patients with VTE have a clinical problem in which there is deep venous thrombosis (DVT) or PTE caused by DVT. In Western nations, the incidence of symptomatic DVT in obstetric patients is reported to be 0.5 to 7 per 1,000 deliveries, and the number has been decreasing slightly in recent years as a result of improved prophylaxis.[1–4] Previously, more than 2/3 of DVT was thought to occur in the puerperal period, particularly in the first week postpartum or the last gestational week, but recent reports describe that DVT can occur at any stage of pregnancy. DVT is 5 times more prevalent in pregnancy than in non-pregnant periods, and occurs 7- to 10-fold more frequently in C/S compared with vaginal deliveries.[4,8,9] Approximately 4% to 5% of obstetrical DVT could lead to PTE, and, conversely, more than 90% of PTE cases are thought to be caused by DVT of the lower extremities.[10] Once PTE occurs it is extremely serious, with a mortality rate reported to be 18–30% if left untreated,[11] and has long been the leading cause of maternal mortalities.[12,13] Likewise, obstetrical PTE in Japan has been increasing, making it the leading cause of direct obstetrical deaths.[7,14,15] Furthermore, most PTE cases are observed in the puerperal period, the majority of them after C/S.[4,16] Pregnancy is conducive to VTE for the following reasons: 1) enhanced coagulation, platelet activation, reduced fibrinolysis, and reduced protein S activity; 2) the venous smooth muscle relaxation effect of estrogen/progesterone; 3) compression of the iliac vein and inferior vena cava by the enlarged gravid uterus; and 4) vascular (particularly endothelial) disorders of the iliac vein region caused by surgical interventions, such as cesarean section and retention of blood caused by postoperative immobilization. In the field of obstetrics, the diseases and conditions that are risk factors are middle-aged pregnancy, prolonged immobilization due to hyperemesis, threatened abortion or threatened premature labor, severe preeclampsia, placenta previa, placental abruption, delivery by cesarean section and marked varix of the lower limbs.[1–4]

There are few reports regarding the incidence of DVT in the gynecology field in Japan. According to research using the ^{125}I-fibrinogen uptake test, Matsumoto et al found that the incidence of postoperative DVT was 10.8% (7/65)

among all gynecological surgeries and 19.4% (6/31) in radical hysterectomy or modified radical hysterectomy[17] which might be a lower rate compared to the West, although by no means a small figure. The risk factors in the field of gynecology are surgeries for giant uterine myoma, giant ovarian tumor, ovarian cancer, uterine cancer and severe pelvic adhesion. Other patients at risk are those with ovarian hyperstimulation syndrome, patients taking oral contraceptives, and postmenopausal patients receiving hormone replacement therapy. Many cases that require long operations with lymphatic resection, massive bleeding or transfusions are also at risk[1–4] According to Nicolaides et al, the incidence of postoperative DVT, including asymptomatic cases, is less than 1–10% in small operations of short duration, 10–40% in moderate risk patients over 40 years of age, and is believed to be 40–80% in high-risk patients with a history of VTE or malignant tumor patients requiring extended surgery. Furthermore, the incidence of fatal PTE is reported to be less than 0.01%, 0.1–0.8% and 1–5%, respectively[18] Japanese data of this kind are currently not available.

In the West, particularly among Caucasians, there is a prevalence of thrombosis caused by genetic structural abnormalities of clotting factors, which is further aggravated by environmental factors to produce a high rate of PTE[19] The Japanese ethnically have fewer structural abnormalities of clotting factors; however, environmental factors, pregnancy and labor, and invasive surgery play a major role in the occurrence of PTE in Japanese[20] As our present survey has shown, PTE has been on the rise in Japan in recent years. In the field of obstetrics and gynecology, PTE has increased by 6.5-fold over the past decade. PTE occurred in 0.02% of total births. The incidence of PTE is 1 per 5,000 births, which is approaching the level of Western countries. The risk of PTE was 22 times higher in C/S compared with vaginal deliveries. The onset period appeared as 3 peaks: early pregnancy, midterm to late pregnancy, and postpartum. PTE onset at early pregnancy could possibly be caused by dehydration and immobilization due to hyperemesis, enhanced coagulation and the formation of thrombophilia. PTE onset in midterm to late pregnancy is believed to be the result of prolonged immobilization due to complications of severe preeclampsia, threatened premature labor, and multiple pregnancies. The postpartum largest peak with the highest incidence on day 1 is attributed to C/S. From the analysis of the onset of PTE in cases with C/S, cesarean delivery itself is thought to be an increased risk of such event. Furthermore, a close relationship between obesity (BMI >27, OR 3.47; BMI >25, OR 1.89) and PTE was observed as well as Western countries. BMI >30 is a risk factor for PTE in Westerners; however, BMI >27 might be characteristic in Japanese pregnant women.

The incidence among gynecological cases was 0.08% of total operations, the risk of PTE, however, was 16 times higher in malignant diseases compared with benign diseases and 7 times higher compared with C/S. In gynecological PTE patients, 15.2% of the cases showed preoperative onsets, and among malignant diseases, 75% of the cases had ovarian cancer. Postoperatively, PTE showed a large peak on day 1 and 2 and subsequently declines; however, some cases were registered as late as 3 weeks postoperatively. Sakuma et al reported that the incidence of PTE was high in patients with ovarian cancer and uterine cancer according to postmortem examination[21] Therefore, careful observation preoperatively and postoperatively is required in gynecological patients, particularly those with malignant diseases. A close relationship between obesity (BMI >25) and PTE was observed in both benign (OR 4.8) and in malignant diseases (OR 2.4) as well as obstetrical patients.

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ORIGINAL ARTICLE

Elevated levels of soluble fibrin in patients with venous thromboembolism

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Abstract The fibrin-related markers (FRMs), including soluble fibrin (SF), D-dimer and fibrin and fibrinogen degradation products (FDP) are considered to be useful for the diagnosis of thrombosis; however, evidence for the diagnosis of thrombosis by SF is still not well established. The present study was designed to evaluate the usefulness of SF in the diagnosis of venous thromboembolism (VTE). The plasma concentrations of FRMs were measured in 551 inpatients suspected to have a VTE. The plasma levels of SF, D-dimer and FDP were significantly higher in patients with VTE than patients without VTE and those were significantly higher in patients without VTE than in healthy volunteers. In a receiver operating characteristic analysis for the diagnosis of VTE, the area under the curve was 0.950 for SF, 0.933 for FDP and 0.805 for D-dimer. The appropriate cut-off values for the diagnosis were as follows SF 5.9 μg/ml, FDP 2.1 μg/ml and D-dimer 4.8 μg/ml. To obtain a 100% negative predictive value for the diagnosis of VTE, the SF was less than 5.2 μg/ml, FDP was less than 1.3 μg/ml, and D-dimer was less than 0.5 μg/ml. Our findings suggest that the SF assay is useful for the diagnosis and exclusion of VTE.

Keywords SF · D-dimer · FDP · VTE · Diagnosis

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1 Introduction

The fibrin-related markers (FRMs) which include fibrin and fibrinogen degradation products (FDP), soluble fibrin (SF) and D-dimer, are sensitive markers for thrombotic diseases [1, 2]. The FRMs are reported to be elevated in deep vein thrombosis (DVT)/pulmonary embolism (PE) [3–5], disseminated intravascular coagulation (DIC) [6–8], acute myocardial infarction (AMI) [9, 10] and thrombotic thrombocytopenic purpura (TTP) [11]. The International Society of Thrombosis and Haemostasis (ISTH) established the diagnostic criteria for overt-DIC using FRM [12]. PE is a common, frequently undiagnosed, and potentially fatal event. Because the symptoms of PE are common, including dyspnoea and chest pain [13–15], the early recognition of DVT [16] and PE [17] by FRM is important clinically.

FDP is the most classical and basic marker of FRM, but the use of FDP is less common than that of D-dimer. D-

dimer is widely used to diagnose thrombosis as DVT but many of the commercially available D-dimer assay kits contain different monoclonal antibodies and standard substances, and are based on different assay systems. Since the issue of the standardization of D-dimer assays remains to be resolved, several studies [18, 19] have reported the basic data for the standardization of D-dimer.

The presence of soluble fibrin (SF) [20] in plasma is an indicator of thrombin activation in the blood, as are the thrombin–antithrombin complex [21] and prothrombin fragment F1 + 2 [21]. Thrombin cleaves fibrinopeptide A and B from the Aα and Bβ chains of fibrinogen, respectively. These are called desAA-fibrin monomer (FM) and desAABB-FM, which polymerize with each other and forms fibrin clots. These molecules in soluble form circulate in the blood are termed as SF. SF mainly consists of desAA-FM or desAABB-FM, which forms a complex with fibrinogen or its derivates [22–24]. Recently, the monoclonal antibody J2–23, which recognizes the epitope within the Aα502–521 region of fibrinogen, was developed for measuring the SF level[25].

The present study was designed to evaluate the usefulness of the SF assay in the diagnosis of thrombosis, such as DVT and PE. For this purpose, we determined the plasma concentration of these molecules in 551 patients suspected of a having venous thromboembolism and 99 healthy volunteers (HV).

2 Materials and methods

2.1 Subjects

From 1 January 2004 to 31 December 2007, 551 patients (median 25–75%) (63, 48–72 years of age; 325 females and 226 males) were suspected of having thrombosis in the hospitals affiliated with Mie University Graduate School of Medicine. The plasma concentrations of fibrin and fibrinogen degradation products (FDP), SF and D-dimer and were examined in these patients and correlated with thrombosis. The study protocol was approved by the Human Ethics Review Committees of the participating institutions and a signed consent form was obtained from each subject. Among these patients, 484 patients (62, 47–71 of age; 278 females and 206 males) did not have any thrombosis, 67 patients had a VTE (DVT or PE) (67, 54–74 years of age; 47 females and 20 males). DVT was diagnosed by either echo or venography and PE was diagnosed by computed tomography, angiography or ventilation-perfusion lung scan.

Among the underlying diseases in these patients, orthopaedic conditions were identified in 117 patients, cancer in 102, cardiovascular diseases in 83, haematological diseases in 55, digestive diseases in 31, autoimmune diseases in 28, respiratory diseases in 21, thrombophilia in 15, no underlying disease in 14, infectious diseases in 10, trauma and burn in 8, and other diseases in 7 (Table 1).

Citrated blood samples were obtained from the peripheral veins of healthy subjects (see below) and patients under fasting conditions and then centrifuged for 20 min at 3,000 rpm. The supernatants (plasma) were analyzed within 4 h. The plasma concentrations of SF and D-dimer were measured in patients with thrombosis at the onset and those without thrombosis at the first consultation. The same parameters were also measured in 99 healthy subjects (mean age 22 years, range 21–30 years; 41 females and 58 males), who were free of any diseases including thrombotic disease or hyperlipidemia as confirmed by an annual medical check-up.

Table 1 Underlying diseases of the subjects

Diseases	Age; median (25th–75th percentile)	Sex (F:M)	DVT (%)
Orthopaedic diseases	61 (34–73)	121:56	24 (13.6)
Cancer	65 (53–74)	42:60	6 (5.9)
Cardiovascular diseases	66 (50–72)	49:34	11 (13.3)
Hematological diseases	59 (36–68)	29:26	1 (1.8)
Digestive diseases	61 (34–73)	15:16	4 (12.9)
Autoimmune diseases	57 (52–63)	23:5	3 (10.7)
Respiratory diseases	62 (43–72)	12:9	0
Thrombophilia	42 (30–60)	12:3	4 (26.7)
No underlying disease	67 (53–76)	10:4	14 (100)
Infectious diseases	65 (49–72)	4:6	0
Trauma/burn	36 (18–60)	3:5	0
Other diseases	36 (32–55)	5:2	0

2.2 Measurement of plasma concentrations of SF, D-dimer and FDP

The plasma levels of SF were determined by the latex agglutination method using Nanopia SF (SEKISUI MEDICAL CO, LTD, Tokyo, Japan) containing monoclonal antibody J2–23 [25]. J2–23 recognizes an epitope in the C-terminal region of the fibrin Aα chain (Aα502–521). The plasma D-dimer and FDP levels were measured by the latex agglutination method using the Nanopia D-dimer and Nanopia P-FDP kits (SEKISUI MEDICAL CO, LTD).

2.3 Statistical analysis

The data are expressed as the median (25–75th% percentile). Differences between the groups were examined for statistical significance using the Mann–Whitney U test while correlations between two variables were tested by Pearson's correlation analysis. P value less than 0.05 denoted a significant difference. The usefulness of D-dimer levels in the diagnosis of thrombosis and VTE was examined by receiver operating characteristic (ROC) analysis [26]. The cut-off values were determined by ROC analysis. All statistical analyses were performed using the SPSS II software package (SPSS Japan, Tokyo).

3 Results

The plasma concentrations of SF were not distributed normally among healthy volunteers; the 95% confidence interval (CI) of SF was from 0 to 5.47 μg/ml. The 95% CIs of D-dimer and FDP in healthy volunteers were from 0.4 to 1.2 μg/ml and from 0.3 to 2.1 μg/ml, respectively. The plasma levels of SF tended to be high in all subjects, especially in those with infectious diseases, those with trauma and burn and those without underlying disease. The plasma levels of D-dimer tended to be high in those with orthopaedic conditions and those without underlying disease, and those of FDP tended to be high in those with infectious diseases and those without underlying disease (Table 2).

The plasma levels of SF were significantly higher in patients with VTE (22.1, 11.4–38.3 μg/ml) than patients without VTE (3.4, 1.9–5.5 μg/ml) and those were significantly higher in those without VTE than in HV ($P < 0.001$, respectively; Fig. 1). The plasma levels of D-dimer were significantly higher in patients with VTE (1.8, 1.0–5.3 μg/ml) than patients without VTE (0.8, 0.5–1.4 μg/l) and those were significantly higher in those without VTE than in HV (0.5, 0.5–0.6 μg/ml) ($P < 0.001$, respectively; Fig. 2). The plasma levels of FDP were significantly higher in patients with VTE (12.2, 7.2–20.8 μg/ml) than patients without VTE (1.4, 0.8–3.5 μg/ml) and those were significantly higher in those without VTE than in HV (0.7, 0.5–1.0 μg/ml) ($P < 0.001$, respectively; Fig. 3).

The relationship between SF and FDP ($Y = 3.804 + 0.911X$, $r = 0.553$) and that between SF and D-dimer ($Y = 5.599 + 0.542X$, $r = 0.543$) were moderately close, and the relationship between FDP and D-dimer ($Y = 2.204 + 0.549X$, $r = 0.905$) was markedly close.

In the ROC analysis for the diagnosis of VTE, the 3 curves of SF, D-dimer and FDP showed convexity at the top. The area under the curve (AUC) was 0.950 in SF, 0.933 in FDP and 0.805 in D-dimer (Fig. 4). The appropriate cut-off values for the diagnosis were as follow: SF 5.9 μg/ml [sensitivity 98.5%, specificity 80.1%, positive predictive value (PPV) 36.3%, negative predictive value (NPV) 99.8% and odds ratio 265.7], FDP 2.1 μg/ml (sensitivity 98.6%, specificity 68.1%, PPV 26.2%, NPV 99.7% and odds ratio 140.9), D-dimer 4.8 μg/ml (sensitivity 28.4%, specificity 96.6%, PPV 48.7%, NPV 92.1% and odds ratio 11.1) (Table 3). In 100% of NPV for the diagnosis of VTE, SF was less than 5.2 μg/ml, FDP was less

Table 2 Plasma levels of SF, D-dimer and FDP in the underlying diseases of the subjects

Diseases	SF (μg/ml)	D-Dimer (μg/ml)	FDP (μg/ml)
Orthopaedic diseases	3.8 (2.4–8.0)	4.9 (1.9–12.9)	0.9 (0.6–1.7)
Cancer	3.4 (1.8–6.2)	0.9 (0.7–1.4)	1.5 (0.9–3.2)
Cardiovascular diseases	3.9 (2.2–10.6)	1.1 (0.5–2.0)	2.2 (0.8–7.5)
Hematological diseases	2.6 (1.2–5.5)	0.7 (0.4–1.2)	1.0 (0.7–2.0)
Digestive diseases	4.4 (2.0–8.4)	0.9 (0.6–1.6)	1.3 (0.8–3.9)
Autoimmune diseases	3.1 (1.7–4.8)	0.6 (0.4–0.9)	1.2 (0.7–3.1)
Respiratory diseases	2.5 (1.0–4.8)	0.6 (0.5–0.9)	1.1 (0.7–1.3)
Thrombophilia	3.8 (1.7–9.4)	0.5 (0.4–1.0)	1.4 (0.7–3.2)
No underlying disease	23.6 (7.0–32.0)	2.1 (1.0–5.3)	10.2 (5.0–19.9)
Infectious diseases	5.8 (1.5–18.3)	1.2 (0.9–2.7)	4.3 (1.8–6.9)
Trauma/burn	10.4 (1.8–12.0)	0.9 (0.7–1.4)	3.4 (1.4–5.6)
Other diseases	2.1 (0.0–4.7)	0.9 (0.6–1.9)	1.5 (1.4–4.1)

Data show the median (25–75%) percentile

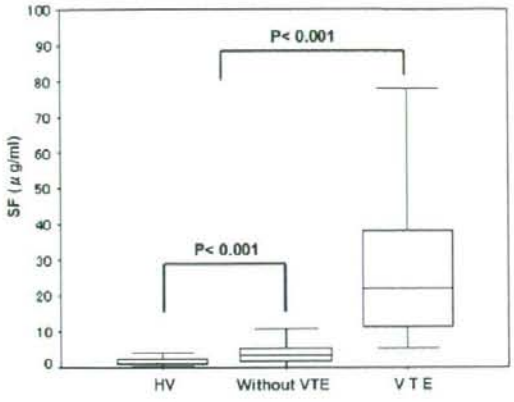

Fig. 1 Plasma concentrations of SF in patients without VTE, those with VTE and healthy volunteers. *VTE* venous thromboembolism, *HV* healthy volunteer

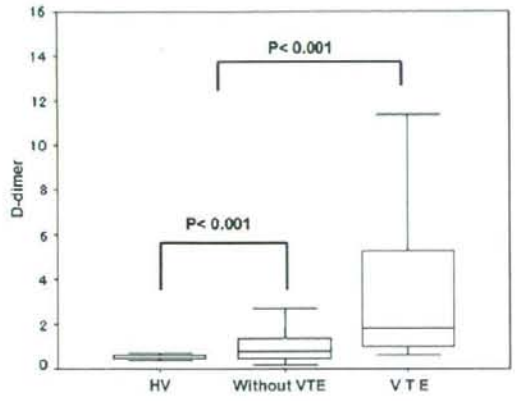

Fig. 2 Plasma concentrations of D-dimer in patients without VTE, those with VTE and healthy volunteers *VTE* venous thromboembolism, *HV* healthy volunteer

than 1.3 μg/ml, and D-dimer was less than 0.5 μg/ml (Fig. 5).

4 Discussion

In the present study, the normal SF level was less than 6.0 μg/ml, and that was similar to the previous reports for other kinds of SF determination [22, 24]. The monoclonal antibodies in the Nanopia SF [25], Iatro SF [24] and Auto LIA FMC [27] assays recognize the α-chain of fibrinogen, which is an important site for the activation of fibrinogen to fibrin by thrombin. The normal range of D-dimer and FDP were from 0.4 to 1.2 μg/ml and from 0.3 to 2.1 μg/ml,

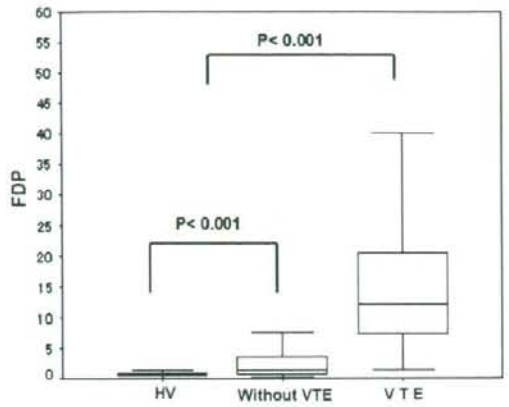

Fig. 3 Plasma concentrations of SF in patients without VTE, those with VTE and healthy volunteers *VTE* venous thromboembolism, *HV* healthy volunteer

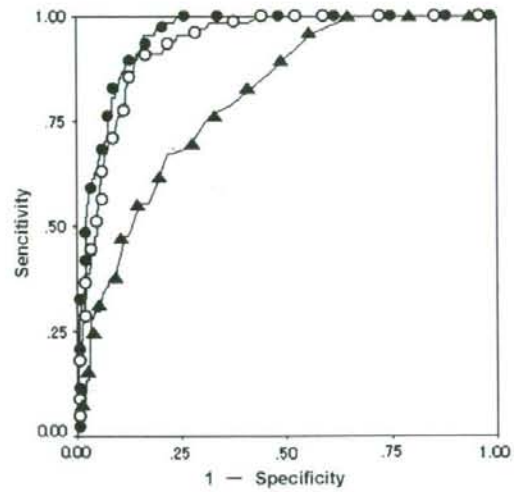

Fig. 4 ROC analysis for diagnosis of VTE. *Closed circle* SF, *open circle* FDP, *closed triangle* D-dimer AUC SF 0.950, FDP 0.933, D-dimer 0.805

respectively. These findings are in agreement with those of previous reports [2, 28].

The plasma levels of SF, D-dimer and FDP were significantly higher in patients with VTE than patients without VTE, suggesting that these FRMs were useful for the diagnosis of VTE. In previous reports [2, 28, 29], the high concentrations of SF and D-dimer could be considered as markers of thrombosis, including VTE. However, no significant difference was observed among those with thrombosis, those with liver transplantation or those with a post operative status [2].