in effective inhibition of the coagulation cascade and inhibition of thrombin generation. Unlike unfractionated heparin (UFH) and low molecular weight heparin (LMWH), fondaparinux is a single chemical entity (1728 Dalton) comprising five saccharides designed specifically to bind to antithrombin [8]. In experimental animal models, fondaparinux was associated with less bleeding than was UFH, at an equivalent antithrombotic concentration [8]. In humans, a therapeutic dose of fondaparinux did not prolong bleeding time [2].

A dose-ranging study in total hip replacement (THR) [16] demonstrated a statistically significant dose-response for the prevention of venous thromboembolism (VTE) in the range from 0.75 mg to 8.0 mg. Moreover, the results suggested that fondaparinux had the potential to improve significantly the risk-benefit ratio for VTE prophylaxis compared with LMWH. Based on the results, a 2.5 mg, once-daily dosage of fondaparinux was selected for the following four phase 3 studies. And these studies [1, 3, 10, 17] demonstrated that a once-daily fondaparinux 2.5 mg significantly improved the risk–benefit ratio for VTE prophylaxis in major orthopaedic surgery of the lower limbs. Eriksson BI et al. [4] reported that 4-week fondaparinux treatment was superior to 1-week fondaparinux in VTE prophylaxis for the patients with hip fracture surgery.

In the United States and Europe, a once-daily subcutaneous dose of 2.5 mg fondaparinux is indicated and used as VTE prophylaxis in fracture surgery, hip/knee replacement surgery and abdominal surgery [12, 15]. In the Seventh American College of Chest Physicians (ACCP) Guidelines on Prevention of VTE [7], fondaparinux, along with LMWH and vitamin K antagonists, was recommended with a Grade 1A rating for VTE prophylaxis in TKR and THR. Fondaparinux were the only anticoagulant recommended with a Grade 1A rating for hip-fracture surgery.

In Japan, UFH and warfarin are indicated for VTE prophylaxis, but there is no randomised clinical trial (RCT) in Japanese patients. LMWH has no indication for VTE prophylaxis. Therefore, no established active control is available in Japan.

These studies was conducted to compare the efficacy and safety of fondaparinux with a placebo, and to evaluate the dose-response relationship between 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux and the incidence of VTE, in TKR or THR surgery.

Methods

Patients

Patients of either gender were eligible if their age was 20 years or greater, and they were scheduled for TKR or THR surgery or revision surgery for TKR or THR. Exclusion criteria were: (a) active, clinically significant bleeding, (b) bleeding tendency/disorder (e.g., ulcer of the digestive tract, diverticulitis of the digestive tract, colitis, acute bacterial endocarditis, severe hypertension, or severe diabetes), (c) severe hepatic disorder, (d) hypersensitivity to UFH or LMWH, (e) requirement of an indwelling intrathecal or epidural catheter during the treatment period (after the first dose of test drug, until the completion of venography), or (f) brain, spine, or ophthalmologic surgery within the 3 months preceding enrollment. Patients with: (g) a body weight less than 40 kg (88 lb), or (h) severe renal disorder (serum creatinine concentration >2.0 mg/dL [180 μmol/L]) were also excluded.

The use of UFH, LMWH, heparinoids, antithrombin agents (argatroban), oral anticoagulants (warfarin), fibrinolytic agents and dextrans was prohibited, beginning 1 week before the first dose of study drug and study period. Nonsteroidal anti-inflammatory drugs (NSAIDs) and antiplatelet medications were also strongly discouraged during the treatment period, but were allowed, if necessary, in a condition of unchanged regimen. During the study, the use of intermittent pneumatic compression or a venous foot pump was prohibited during surgery, and continuous spinal and epidural anaesthesia (intrathecal or epidural catheterisation) were prohibited, beginning 2 hours before the first dose of study drug and study period.

Study design

There are two studies described in this paper, Study 1 for TKR and Study 2 for THR, both of which are multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose–response studies of subcutaneous fondaparinux.

The studies were conducted according to the provisions of the revised Declaration of Helsinki and the guidelines for Good Clinical Practice. The study protocols were approved by the institutional review board (IRB) at each centre. Written informed consent was obtained from each patient before enrollment in the trial. A Central Independent Adjudication Committee for Efficacy (CIACE) evaluated diagnostic images in a blind manner for the incidence of VTE. A Central Independent Adjudication Committee for Safety (CIACS) evaluated all reported bleeding events and adverse events (AEs), also in a blind manner.

Outcome measures

The primary efficacy outcome was assessed by the rate of VTE [defined as deep vein thrombosis (DVT), pulmonary

Table 1 Summary of demographic characteristics: all-treated-patients population

						n (%)
Study 1 (TKR)						
Parameter	**Placebo**			**Fondaparinux**		
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=87	*n*=86	*n*=85	*n*=84	*n*=84	*n*=426
Gender						
Female	72 (82.8)	71 (82.6)	67 (78.8)	67 (79.8)	74 (88.1)	351 (82.4)
Age, y ± (SD)						
	70.4±7.9	71.4±8.7	70.5±8.0	71.2±7.8	71.5±7.6	71.0±8.0
Weight, kg ± (SD)						
	58.94±9.80	57.87±10.71	59.99±10.16	59.14±9.88	59.30±8.43	59.05±9.81
Height, cm (SD)						
	150.51±7.59	150.91±7.55	151.45±6.96	150.15±6.85	150.04±6.45	150.61±7.09
BMI, kg/m²						
<30	79 (90.8)	73 (84.9)	70 (82.4)	69 (82.1)	71 (84.5)	362 (85.0)
>=30	8 (9.2)	13 (15.1)	15 (17.6)	15 (17.9)	13 (15.5)	64 (15.0)
Baseline creatinine clearance, mL/min						
<30	2 (2.3)	1 (1.2)	1 (1.2)	1 (1.2)	0	5 (1.2)
30 – 50	7 (8.0)	10 (11.6)	12 (14.1)	12 (14.3)	10 (12.0)	51 (12.0)
50 – 80	44 (50.6)	44 (51.2)	43 (50.6)	37(44.0)	41 (49.4)	209 (49.2)
>=80	34 (39.1)	31 (36.0)	29 (34.1)	34 (40.5)	32 (38.6)	160 (37.6)
Missing	0	0	0	0	1	1
Type of surgery						
Primary	82 (94.3)	85 (98.8)	84 (98.8)	84 (100)	80 (95.2)	415 (97.4)
Revision	5 (5.7)	1 (1.2)	1 (1.2)	0	4 (4.8)	11 (2.6)
Study 2 (THR)						
Parameter	**Placebo**			**Fondaparinux**		
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=82	*n*=80	*n*=80	*n*=81	*n*=83	*n*=406
Gender						
Female	64 (78.0)	69 (86.3)	60 (75.0)	74 (91.4)	66 (79.5)	333 (82.0)
Age, y ± (SD)						
	62.3±12.4	60.8±9.8	60.9±10.1	61.5±10.8	62.7±11.4	61.6±10.9
Weight, kg ± (SD)						
	56.31±9.40	55.81±9.61	60.21±9.73	54.19±8.61	56.20±11.28	56.54±9.92
Height, cm (SD)						
	153.20±8.24	152.38±7.55	154.58±7.92	150.96±6.88	152.35±7.00	152.69±7.59
BMI, kg/m²						
<30	77 (93.9)	73 (91.3)	73 (91.3)	79 (97.5)	78 (94.0)	380 (93.6)
>=30	5 (6.1)	7 (8.8)	7 (8.8)	2 (2.5)	5 (6.0)	26 (6.4)
Baseline creatinine clearance, mL/min						
30 – 50	7 (8.9)	6 (7.6)	1 (1.3)	5 (6.2)	5 (6.0)	24 (6.0)
50 – 80	30 (38.0)	28 (35.4)	27 (34.6)	36 (44.4)	31 (37.3)	152 (38.0)
>=80	42 (53.2)	45 (57.0)	50 (64.1)	40 (49.4)	47 (56.6)	224 (56.0)
Missing	3	1	2	0	0	6
Type of surgery						
Primary	76 (92.7)	72 (90.0)	76 (95.0)	74 (91.4)	79 (95.2)	377 (92.9)
Revision	6 (7.3)	8 (10.0)	4 (5.0)	7 (8.6)	4 (4.8)	29 (7.1)

BMI: body mass index; THR: total hip replacement; TKR: total knee replacement

embolism (PE), or both] up to day 11. Patients were examined for deep-vein thrombosis by systematic bilateral ascending venography of the legs between day 11 and day 17, but no more than 2 days after the last injection of study drug, or earlier if thrombosis was clinically suspected. Symptomatic PE was confirmed by a lung scan indicating a high probability of PE, pulmonary angiography, or helical computed tomography, or at autopsy.

The primary safety outcome was the incidence of major bleeding, which included fatal bleeding; bleeding that was retroperitoneal, intracranial, or intraspinal or that involved any other critical organ; bleeding leading to reoperation; and overt bleeding with a bleeding index of 2 or more. The bleeding index was calculated as the number of units of packed red cells or whole blood transfused plus the haemoglobin values before the bleeding episode minus the haemoglobin values after the episode (in grams per decilitre).

Treatment and regimen

Patients were assigned to receive a once-daily subcutaneous injection of fondaparinux (0.75 mg, 1.5 mg, 2.5 mg, or 3.0 mg) or placebo. Treatment was scheduled from Day 2 to Days 11–15 (at least 10 days, with the day of surgery defined as Day 1).

The first dose of study drug was administered at 24±2 h after surgery, before 11:00 pm on Day 2; subsequent doses were administered at 9:00 am ± 2 h, from Days 3 to 15. The first dose on Day 2 and the second dose on Day 3 were at least 12 hours apart.

Disposable pre-filled syringes containing 0.75 mg, 1.5 mg, 2.5 mg, or 3.0 mg of fondaparinux or placebo were supplied by Sanofi-Winthrop Industrie (Notre Dame de Bondeville, France). Fondaparinux and placebo were provided as isotonic solutions in 0.25 ml, and placebo was isotonic sodium chloride. All pre-filled syringes were indistinguishable from one another.

Results

Disposition of patients

Study 1

Study 1 was conducted from October 2001 to August 2003 at 56 centres in Japan. A total of 432 patients were enrolled and randomised. Six of the 432 patients did not receive any study drug and were excluded from further analyses, with 426 patients remaining in the "all treated patients" (ATP) population (339 in the fondaparinux groups and 87 in the placebo group). A total of 29 (6.8%) withdrew. There were no statistically significant differences in values for demographic variables (Table 1) among the five treatment groups. The physical prophylaxis during the study is summarised in Table 2.

Study 2

Study 2 was conducted from October 2001 to June 2003 at 57 centers in Japan. A total of 411 patients were enrolled and randomised. Five out of 411 patients did not receive any

Table 2 Summary of patients who used physical methods for DVT prophylaxis from surgery to end of treatment: all-treated-patients population

n (%)

Study 1 (TKR)						
Parameter	**Placebo**	**Fondaparinux**				
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=87	*n*=86	*n*=85	*n*=84	*n*=84	*n*=426
Elastic stocking/bandage (%)						
No elastic stocking/bandage	26 (29.9)	28 (32.6)	33 (38.8)	26 (31.0)	31 (36.9)	144 (33.8)
Used elastic stocking/bandage 1–10 days	33 (37.9)	36 (41.9)	31 (36.5)	35 (41.7)	34 (40.5)	169 (39.7)
Used elastic stocking/bandage 11 days or more	28 (32.2)	22 (25.6)	21 (24.7)	23 (27.4)	19 (22.6)	113 (26.5)
Study 2 (THR)						
Parameter	**Placebo**	**Fondaparinux**				
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**	**Total**
	n=82	*n*=80	*n*=80	*n*=81	*n*=83	*n*=406
Elastic stocking/bandage (%)						
No elastic stocking/bandage	40 (48.8)	40 (50.0)	40 (50.0)	41 (50.6)	38 (45.8)	199 (49.0)
Used elastic stocking/bandage 1–10 days	20 (24.4)	24 (30.0)	21 (26.3)	25 (30.9)	29 (34.9)	119 (29.3)
Used elastic stocking/bandage 11 days or more	22 (26.8)	16 (20.0)	19 (23.8)	15 (18.5)	16 (19.3)	88 (21.7)

DVT: deep vein thrombosis; THR: total hip replacement; TKR: total knee replacement

study drug and were excluded from further analyses, with 406 patients remaining in the ATP population (324 in the fondaparinux groups and 82 in the placebo group). A total of 25 (6.2%) withdrew. There were no statistically significant differences in the values for demographic variables (Table 1) among the five treatment groups. The use of physical prophylaxis is summarised in Table 2.

Efficacy

Study 1 (TKR)

In the intent to treat (ITT) population, 65.3%, 34.2%, 21.3%, 16.2% and 9.5% of the patients showed VTE in the groups given placebo, 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux respectively. The Cochran-Armitage trend test demonstrated a statistically significant difference ($P<0.001$) in VTE incidence by fondaparinux, compared with placebo (Fig. 1). VTE incidence in all groups receiving fondaparinux was significantly lower ($P<0.001$) than in the group receiving placebo, by Fisher's exact probability tests. The calculated relative risk reductions (RRR) of VTE with 0.75 mg, 1.5 mg, 2.5 mg and 3.0 mg of fondaparinux, compared with placebo, were 47.6%, 67.4%, 75.2%, and 85.5% respectively.

Study 2 (THR)

In the ITT population, 33.8%, 24.2%, 4.6%, 7.4% and 14.3% of the patients showed VTE in the groups receiving placebo, 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux respectively. The Cochran-Armitage trend test demonstrated a statistically significant reduction ($P<0.001$) in VTE incidence by fondaparinux, compared with placebo (Fig. 1). The groups receiving 1.5 mg, 2.5 mg, or 3.0 mg fondaparinux were significantly lower ($P<0.01$, $P<0.01$ and $P=0.007$ respectively) from the placebo group by Fisher's exact probability tests. RRR of VTE with 0.75 mg, 1.5 mg, 2.5 mg and 3.0 mg of fondaparinux were 28.4%, 86.4%, 78.1%, and 57.7% respectively, compared with placebo.

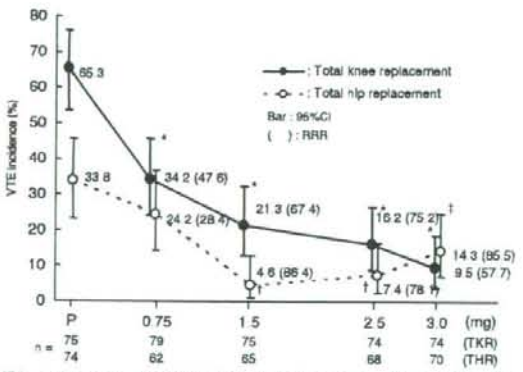

Fig. 1 Venous thromboembolism: incidence in all groups. *VTE*: venous thromboembolism; *TKR*: total knee replacement; *THR*: total hip replacement; *RRR*: relative risk reduction * $P<0.001$, † $P<0.01$, ‡ $P=0.007$ (Fisher's exact probability test)

Safety evaluation

The incidences of major and minor bleeding are presented Table 3. In the studies, major bleeding during the treatment period was the primary safety endpoint.

In Study 1 (TKR), the incidence of major bleeding was 1.1% with placebo and 0%, 0%, 1.2%, and 1.2% with 0.75 mg, 1.5 mg, 2.5 mg, and 3.0 mg of fondaparinux respectively. The incidences of major or minor bleeding among the treatment groups were not statistically significant; there was no fatal bleeding, bleeding in a critical organ, or bleeding leading to re-operation. All of the patients who experienced major bleeding received >2 units of blood. Two patients treated with fondaparinux had bleeding at the surgical site. One patient in the placebo group had major bleeding in the gastrointestinal tract.

There were no deaths during the study; three severe AEs were reported in two patients. One patient (receiving fondaparinux 3.0 mg) experienced skin necrosis that was not considered by the investigator to be related to the study drug; another patient (receiving placebo) developed a gastric ulcer and had a gastrointestinal hemorrhage. Both patients recovered without sequelae from these events.

There was no statistically significant difference in drug-related AEs among treatment groups.

In Study 2 (THR), there were no statistically significant differences in major or minor bleeding events between the fondaparinux groups and the placebo group. The incidences of major and minor bleeding events by fondaparinux were not dose-dependent. Three cases of major bleeding included a reduction in haemoglobin of >2 g/dL in one patient (receiving fondaparinux 2.5 mg) and transfusion of more than two units of blood in two patients (receiving fondaparinux 0.75 mg, 2.5 mg). No fatal bleeding occurred. Furthermore, although clinically abnormal blood loss occurred in more patients in the 2.5 mg fondaparinux group, all abnormal blood loss in this group was considered to be associated with surgery and not related to fondaparinux treatment.

There were no deaths during the study; however, three severe AEs were reported in two patients. One patient (0.75 mg fondaparinux) had hepatic dysfunction on Day 4 that was not related to test drug. The second patient (0.75 mg fondaparinux) experienced a cerebral infarction and supra-

Table 3 The proportion of patients with bleeding by treatment group: all-treated-patients population, Study 1 (TKR)

Study 1 (TKR)					
Types of bleeding (%)	**Placebo**	**Fondaparinux**			
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**
	n=87	*n*=86	*n*=85	*n*=84	*n*=84
Major bleeding	1 (1.1)	0	0	1 (1.2)	1 (1.2)
	[0.0 – 6.2]	[0.0 – 4.2]	[0.0 – 4.2]	[0.0 – 6.5]	[0.0 – 6.5]
Minor bleeding only	3 (3.4)	0	5 (5.9)	2 (2.4)	3 (3.6)
	[0.7 – 9.7]	[0.0 – 4.2]	[1.9 – 13.2]	[0.3 – 8.3]	[0.7 – 10.1]
Any bleeding	4 (4.6)	0	5 (5.9)	3 (3.6)	4 (4.8)
	[1.3 – 11.4]	[0.0 – 4.2]	[1.9 – 13.2]	[0.7 – 10.1]	[1.3 – 11.7]
Any bleeding Cochran-Armitage (P)[a]			*0.57*		
Study 2 (THR)					
Types of bleeding (%)	**Placebo**	**Fondaparinux**			
		0.75 mg	**1.5 mg**	**2.5 mg**	**3.0 mg**
	n=82	*n*=80	*n*=80	*n*=81	*n*=83
Major bleeding	0	1 (1.3)	0	2 (2.5)	0
	[0.0 – 4.4]	[0.0 – 6.8]	[0.0 – 4.5]	[0.3 – 8.6]	[0.0 – 4.3]
Minor bleeding only	0	3 (3.8)	2 (2.5)	4 (4.9)	0
	[0.0 – 4.4]	[0.8 – 10.6]	[0.3 – 8.7]	[1.4 – 12.2]	[0.0 – 4.3]
Any bleeding	0	4 (5.0)	2 (2.5)	6 (7.4)*	0
	[0.0 – 4.4]	[1.4 12.3]	[0.3 – 8.7]	[2.8 – 15.4]	[0.0 – 4.3]
Any bleeding Cochran-Armitage (P)[a]			*0.54*		

n (%), [95% CI]

A significant dose-response relationship in bleeding was not observed with the 0.75 mg to 3.0 mg fondaparinux dose range in either of the studies.

[a] Comparisons across all 5 treatment populations, using the values of the doses as score (0, 0.75, 1.5, 2.5, and 3.0)

*P=0.013 vs placebo group

THR: total hip replacement; TKR: total knee replacement

ventricular tachycardia on Day 5 but recovered; both events were considered possibly related to the test drug.

Discussion

In both studies, fondaparinux groups demonstrated significant dose-dependent effect in VTE incidence. 1.5 mg and 2.5 mg fondaparinux respectively reduced risk of VTE by 67.4% and 75.2% in the THR study, and that of VTE by 86.4% and 78.1% in the TKR study, compared with placebo. Fondaparinux also showed a good safety profile, in terms of bleeding complication, and the incidences of bleeding events by fondaparinux were not dose-dependent in both the TKR and THR studies.

In the United States, VTE is recognised as a silent, life-threatening disease and VTE prophylaxis is considered critical in a variety of medical settings, not only in postsurgical patients but also in acutely ill medical patients [7]. It is estimated that there are approximately 2 million cases of DVT and 600,000 cases of PE—including 60,000 fatal cases—per year in the United States [9]. In contrast, in Japan, 3,492 PE cases were estimated in 1996, based on surveillance by the Japanese Government [13, 14]. Because of the reported lower incidence of VTE in Japan, the importance of VTE prophylaxis has not been well-recognised by Japanese physicians.

Recently, Fujita et al. reported that, similar to Western data, VTE incidences of 48.6% and 22.6% followed TKR and THR surgery respectively, in Japanese patients [5].

According to the Sixth ACCP Guidelines [6], overall RRR of VTE following TKR surgery was 33% with low-dose UFH (two studies) and 52% with LMWH (13 studies), and the overall RRR of VTE following THR surgery was 45% with low dose UFH (11 studies) and 70% with LMWH (30 studies).

In Study 2 for THR, the incidence of VTE in both the 2.5 mg and 3.0 mg fondaparinux groups was slightly higher than that of the 1.5 mg group. However, there were no statistically significant differences among these groups; therefore, these differences could be observed by chance. There were no differences in demographic or VTE risk factors among the groups; however, there were more patients with ischaemic heart disease or diabetes in the 3.0 mg group, and it is speculated that these disorders may affect the efficacy of anticoagulant therapy. The incidences of VTE with 1.5 mg to 2.5 mg of fondaparinux in Study 2 for THR are similar to those in other published reports [1, 3, 10, 17].

The efficacies of these studies were completely equal to that in the United States and Europe. Major bleeding associated with fondaparinux was reported in 2.1% (11/517) of patients undergoing TKR [1], and 1.8% [17] and 4.1% [10] in THR; however, fatal bleeding or critical organ bleeding was not reported in Western studies. In the present studies, major bleeding occurred in one patient (0.6%) in the placebo group, one patient (0.6%) at 0.75 mg, 3 (1.8%) at 2.5 mg, and one patient (0.6%) at 3.0 mg of fondaparinux. The incidences of major bleeding in Japanese studies were somewhat lower than in the United States and Europe. It is considered that lower incidence of major bleeding could be due to the initial administration fondaparinux 24 hours after operation. Compared with overseas data, the efficacy and safety findings in this study support a once-daily dose of 2.5 mg fondaparinux is favorable for VTE prophylaxis in Japanese patients undergoing TKR or THR.

Finally, our study demonstrated that fondaparinux effectively prevents VTE without increasing the risk of bleeding or other AEs in patients undergoing TKR or THR. Fondaparinux could be a promising option for the prevention of VTE major orthopedic surgery of the lower limbs.

Conclusion

1) The incidence of VTE in Japanese TKR and THR patients are similar to Western data.
2) Once-daily, subcutaneous doses of 1.5 mg to 2.5 mg fondaparinux have a favourable risk (bleeding and other AEs) to benefit (VTE prevention) ratio in these patients.
3) Fondaparinux, the first in a new class of anticoagulants, could be one of the best options for managing the risk of VTE in patients at major orthopaedic surgery of the lower limbs.

In order to define optimal daily dose of fondaparinux for Japanese patients, further clinical study is needed.

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Gender Differences in Chronic Thromboembolic Pulmonary Hypertension in Japan

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Background The predominance of chronic thromboembolic pulmonary hypertension (CTEPH) in females and association of HLA-B*5201 with CTEPH have been reported in Japan. However, the clinical characteristics of female CTEPH remain uncertain. The purpose of the present study is to clarify the clinical phenotype of female CTEPH in Japan.

Methods and Results The 150 consecutive patients (female 103, male 47; age 52.8±12.4 years SD) were admitted to Chiba University Hospital, and diagnosis was confirmed using right cardiac catheterization and pulmonary angiography. Among these patients, 78 underwent pulmonary endarterectomy. Clinical characteristics, pulmonary hemodynamics, extent of central disease and surgical outcome in females were compared with those in males. The female patients were elderly and had less deep vein thrombosis, less acute embolic episodes, better cardiac function, lower arterial oxygen tension and more peripheral thrombi, and showed less improvement through surgery than males. When the patients were identified using HLA-B*5201, HLA-B*5201-positive female patients had less embolic episodes and better cardiac function with lower operative mortality. In contrast, HLA-B*5201-negative female patients had less embolic episodes, and more peripheral thrombi, resulting in less improvement by surgery.

Conclusion The clinical phenotype of female CTEPH differed from that of male CTEPH. Additionally, gender differences of HLA-B*5201-positive type were dissimilar to those of HLA-B*5201-negative type. (*Circ J* 2008; **72:** 2069–2074)

Key Words: Chronic thromboembolic pulmonary hypertension; Gender difference; HLA; Pulmonary embolism

Chronic thromboembolic pulmonary hypertension (CTEPH) has been considered to be caused by single or recurrent pulmonary emboli arising from deep vein thrombosis (DVT)[1,2] However, the incidence of DVT in this disease is only 35 to 45% in the USA and 12 to 38% in Japan[2–6] It was reported that the risk of recurrent venous thromboembolism was higher in men than women[7] The female-to-male ratio in CTEPH was 2.1 in Japan, which is much higher than that of 0.7 in the USA[3,8] However, the incidence of DVT in females was similar to that in males, even in Japan[9] Jamieson reported a female predominance in type 3 disease (distal segmental arteries only type)[10] In addition, we previously reported that female predominant CTEPH without DVT exists in Japan, and that the disease was associated with HLA-B*5201 and HLA-DPB1*0202. HLA-B*5201-positive patients were predominantly female, and this was unrelated to DVT[11]

It remains uncertain whether the clinical phenotype in female CTEPH differed from male CTEPH, especially in the Japanese series.

The purpose of the present study is to clarify the clinical phenotype in female CTEPH in Japan. We also examined the clinical phenotype of female CTEPH when patients were analysed according to HLA-B*5201 status because the HLA-B*5201-positive type could indicate a female-predominant Japanese-specific type, while the HLA-B*5201-negative type could indicate a DVT-related type similar to Western countries. Because of the female predominance in HLA-B*5201 patients, gender differences in the clinical parameters might be more related to the HLA-B*5201-positive type than the female gender itself. We added multivariate analysis to clarify whether female gender or HLA-B*5201 had the main effects on clinical parameters.

Methods

Study Subjects

We studied 150 patients, 103 females and 47 males, with CTEPH, diagnosed at Chiba University Hospital, Chiba, Japan. CTEPH was defined as mean pulmonary arterial pressure (Ppa) >25 mmHg with normal wedge pressure in patients with symptoms for >6 months. Chronic thromboembolic findings were confirmed using pulmonary angiography. All patients were examined using blood gas examination, right-heart catheterization, pulmonary angiography and computed tomographic angiography. Seventy-eight of the patients underwent pulmonary endarterectomy.

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Table 1 Clinical Characteristics of All Patients With CTEPH (n=150)

Age (years)	*52.8±12.4*
F/M (n)	*103/47*
Acute embolic episodes (%)	*45.3*
Underlying disease	
DVT (%)	*38.7*
Pelvic surgery (%)	*13.3*
Coagulopathy (%)	*31.3*
(Anti-cardiolipin antibody) (%)	*24.7*
Malignancy (%)	*4.0*
Heart disease (%)	*7.3*
*HLA-B*5201 (%)*	*31.3*
Cardiorespiratory variables	
Mean Pra (mmHg)	*5.2±4.4*
Mean Ppa (mmHg)	*44.2±11.1*
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	*2.54±0.63*
PVR ($dynes \cdot s \cdot cm^{-5}$)	*827±382*
PaO_2 (Torr)	*58.6±9.8*
WHO functional classification I/II/III/IV	*2/37/97/14*

Values are mean±SD or n (%).
CTEPH, chronic thromboembolic pulmonary hypertension; DVT, deep vein thrombosis; Pra, right atrium pressure; Ppa, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PaO_2, arterial oxygen tension.

Measurements

At least 3 months after an acute episode, pulmonary hemodynamics, cardiac output (using thermodilution technique) and blood gases were measured in the supine position while breathing normally. The cardiac index was calculated as cardiac output divided by body surface area. Pulmonary vascular resistance (PVR) was calculated conventionally as the ratio of the difference between mean Ppa and pulmonary wedge pressure to cardiac output. Cardiorespiratory variables were also measured after surgery. To evaluate the effectiveness of surgery, the % decrease in PVR was calculated using [preoperative PVR−postoperative PVR]×100 (%)/preoperative PVR.

HLA Typing

HLA typing was analyzed in 126 patients. Serological HLA typing of A and B antigens was done using a standard microcytotoxicity test.[12] Genomic DNA was obtained from peripheral blood leukocytes using a QIAamp DNA blood minikit (Qiagen). DNA typing of HLA-B and –DPB1 genes was performed using a RELI-typing kit (Dynal) and/or using SSO probes as previously reported.[13,14]

Assessment of Central Extent of Thrombi

Using the Bergin's method, central arteries were defined as vessels proximal to the segmental branches and were divided into 4 portions. These portions included the right and left main pulmonary arteries proximal to the upper lobe branches and the right and left descending portions of the central arteries between the upper lobes and the segmental branches. The central disease score was quantified by adding up the number of abnormal central portions in each patient up to a maximum score of 4.[15] Two investigators retrospectively calculated the scores independently by workstation, and if the score differed, it was changed to either one score up or down by consensual agreement of the 2 investigators.

During the operation, thromboembolic disease was visualized and each patient was classified into one of 4 groups as reported by Thistlethwaite (intraoperative classification): type 1, fresh thrombus in the main-lobar pulmonary arteries; type 2, intimal thickening and fibrosis proximal to the segmental arteries; type 3, disease within distal segmental arteries only; and type 4, distal arteriolar vasculopathy without visible thromboembolic disease.[16]

Pulmonary Endarterectomy

The selection criteria for pulmonary thromboendarterectomy were slightly modified from those defined by Moser.[17] Our criteria were: (1) mean Ppa >30 mmHg, resulting in calculated PVR >300 $dynes \cdot s \cdot cm^{-5}$ even after oral anticoagulant therapy for >6 months; (2) WHO functional class ≥3; (3) thrombi defined as accessible to current surgical techniques (presence at main, lobar, segmental arteries); and (4) absence of severe associated disease.[4,18] Although we have used a lateral thoracotomy in 16 previous cases, since 1990 we used median sternotomy with the application of deep hypothermia and circulatory arrest in 62 cases.[4,19]

The Human Subject Committee of Chiba University approved the study, written informed consent was obtained from all patients and the study protocol for HLA typing was approved by the Research Ethics Committee of Chiba University School of Medicine.

Clinical characteristics were compared between males and females in all patients, and in patients with or without HLA-B*5201, respectively.

Statistical Analysis

Comparison of males and females was performed using unpaired Student's t-test when data were continuous variables, and by chi-square test or Mann-Whitney test when data were categorical, where appropriate. We performed a 2-way factorial analysis of variance (ANOVA) for parametric data and multiple regression analysis for categorized data, using gender and HLA-B*5201 as independent variables, and other clinical parameters as dependent variables. A p-value<0.05 was considered significant.

Results

Patient Characteristics

Characteristics of the patients are shown in Table 1. There were more female (n=103) than male patients (n=47). Age at catheterization varied from 18 to 78 years, with a mean±SD of 52.8±12.4. Sixty-eight patients (45.3%) had a history of acute embolic episodes. Fifty-eight patients (38.7%) had a history of DVT. Forty-seven patients (31.3%) revealed abnormalities in the screening for coagulopathy. Thirty-seven patients (24.7%) were diagnosed with antiphospholipid syndrome. Mean Ppa, cardiac index, PVR and PaO_2 were 44.2±11.1 mmHg, 2.54±0.63 $L \cdot min^{-1} \cdot m^{-2}$, 827±382 $dynes \cdot s \cdot cm^{-5}$ and 58.6±9.8 Torr, respectively. The patients were classified as WHO functional class I (n=2), class II (n=37), class III (n=97) and class IV (n=14).

Comparison of Clinical Characteristics Between Males and Females

As shown in Table 2, female patients were significantly older than males (54.3±11.3 vs 49.6±14.1 years, p=0.03). Female patients showed significantly less acute embolic episodes (34.0 vs 70.2%, p<0.001) and less history of DVT (31.1 vs 55.3%, p=0.005) compared with males. Female patients had a significantly greater history of pelvic surgery compared with males (19.4 vs 0.0%, p=0.012), while females had significantly less heart disease than males (3.9 vs 14.9%, p=0.016).

The cardiac index was significantly higher in females than in males (2.65±0.62 vs 2.36±0.66 $L \cdot min^{-1} \cdot m^{-2}$, p=0.01), and

Table 2 Gender Differences of Clinical Characteristics in CTEPH Patients

	Female (n=103)	Male (n=47)	p value
Age (years)	54.3±11.3	49.6±14.1	0.03
Acute embolic episodes (%)	34.0	70.2	<0.001
Underlying disease			
DVT (%)	31.1	55.3	0.005
Pelvic surgery (%)	19.4	0.0	0.012
Coagulopathy (%)	27.1	40.4	0.105
(Anti-cardiolipin antibody) (%)	23.2	30.4	0.35
Malignancy (%)	1.9	8.5	0.057
Heart disease (%)	3.9	14.9	0.016
HLA-B*5201 (%)	41.6	27.0	0.124
Haemodynamics			
Pra (mmHg)	4.3±3.5	7.1±5.5	0.0002
Mean Ppa (mmHg)	44.8±11.1	43.0±11.3	0.36
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.65±0.62	2.36±0.66	0.01
PVR ($dynes \cdot s \cdot cm^{-5}$)	850±393	777±357	0.28
PaO_2 (Torr)	56.4±9.8	61.7±9.8	0.005
Location of thrombi			
Central disease score	1.09±1.01	1.83±1.27	0.0002
Intra-operative classification			
Type 1/2/3/4	29/10/8/0	28/0/2/1	
Non-type 1 (%)	38.3	9.7	0.005
WHO functional classification I/II/III/IV	1/23/69/10	1/14/28/4	0.71

Values are mean±SD or n (%).
Abbreviations see in Table 1.

Table 3 Gender Differences for Surgical Outcome by Pulmonary Endarterectomy

	Female (n=47)	Male (n=31)	p value
Operative mortality (%)	11	23	0.15
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	406±282	257±119	0.02
% decrease in PVR (%)	51.9±25.4	65.2±21.4	0.04

Values are mean±SD or n (%).
% decrease in PVR, [preoperative PVR-postoperative PVR]×100(%)/preoperative PVR. Other abbreviation see in Table 1.

mean right atrial pressure (Pra) was significantly lower in females than in males (4.3±3.5 vs 7.1±5.5 mmHg, p=0.0002). However, PaO_2 in females was significantly lower than in males (56.4±9.8 vs 61.7±9.8 Torr, p=0.005).

With regard to the WHO functional classification, there was no significant difference between females and males.

Central disease score in females was significantly lower than in males, indicating a peripheral type (1.09±1.01 vs 1.83±1.27, p=0.0002). With regard to intra-operative classification, female patients showed significantly more non-type 1 disease compared with male patients (38.3 vs 9.7%, p=0.005).

Surgical Outcome and Gender

Although there was no significant difference in mortality between males and females, postoperative PVR in females was significantly higher than in males (406±282 vs 257±119 $dynes \cdot s \cdot cm^{-5}$, p=0.02), and the percentage decrease in PVR in females was significantly less than in males (51.9±25.4 vs 65.2±21.4%, p=0.04) (Table 3).

*Association With Gender Differences in Clinical Characteristics and HLA-B*5201*

As shown in Table 4, in HLA-B*5201-positive patients, females showed less embolic episodes (27.0 vs 80.0%, p=0.002). The cardiac index in females was significantly higher than in males (2.77±0.61 vs 2.23±0.38 $L \cdot min^{-1} \cdot m^{-2}$, p=0.001), and mean Pra in females was significantly lower than in males (3.9±3.7 vs 8.2±5.9 mmHg, p=0.0006). The surgical mortality was significantly lower in females than in males (0 vs 40%, p=0.0098).

In contrast, as shown in Table 5, in HLA-B*5201-negative patients, female CTEPH patients had less embolic episodes (40.4 vs 66.7%, p=0.03), lower central disease score (0.93±0.98 vs 2.04±1.32, p<0.0001) and more non-type 1 disease (48.0 vs 0.0%, p=0.0005), indicating the peripheral type of emboli. As a result, female patients showed higher postoperative PVR (405±303 vs 234±115 $dynes \cdot s \cdot cm^{-5}$, p=0.05) and a modest percentage decrease in PVR compared with males (55.6±21.3 vs 69.9±18.3%, p=0.04).

Two-way factorial ANOVA and multiple regression analysis revealed that the HLA-B*5201-positive type was significantly correlated with the absence of DVT (p=0.005), but female gender was not correlated with the absence of DVT (p=0.06). HLA-B*5201 did not show any correlation with any other clinical parameters (p>0.10). In contrast, female gender correlated with the absence of acute embolic episodes (p=0.0007), higher cardiac index (p=0.01), lower mean Pra (p<0.0001), lower central disease score (p=0.03) and non-type 1 disease (p=0.01).

Differences of Clinical Phenotype in Female CTEPH Based on HLA Types

To identify the differences of clinical phenotype of female

Table 4 Characteristics of Gender Difference in HLA-B*5201-Positive Type

	Female (n=37)	Male (n=10)	p value
Age (years)	53.9±10.5	50.4±18.9	0.45
DVT (%)	13.5	40.0	0.06
Embolic episode (%)	27.0	80.0	0.002
Pra (mmHg)	3.9±3.7	8.2±5.9	0.0006
Mean Ppa (mmHg)	43.7±11.3	44.6±12.2	0.79
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.77±0.61	2.23±0.38	0.001
PVR ($dynes \cdot s \cdot cm^{-5}$)	837±460	857±396	0.86
PaO_2 (Torr)	57.1±10.5	63.2±9.8	0.04
Central disease score	1.24±0.98	1.50±1.08	0.48
Intraoperative classification			
Type 1/2/3/4	13/1/1/0	4/0/0/1	
Non-type 1	13.3	20.0	0.72
Operative mortality (%)	0.0	40.0	0.0098
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	365±223	232±112	0.34
% decrease in PVR (%)	53.7±25.5	65.6±23.2	0.46

Values are mean±SD or n (%).
Abbreviations see in Tables 1,3.

Table 5 Characteristics of Gender Difference in HLA-B*5201-Negative Type

	Female (n=52)	Male (n=27)	p value
Age (years)	54.2±11.6	53.1±11.4	0.71
DVT (%)	42.3	55.6	0.26
Embolic episode (%)	40.4	66.7	0.03
Pra (mmHg)	4.6±3.3	6.3±5.1	0.07
Mean Ppa (mmHg)	45.8±10.9	41.9±10.6	0.12
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.59±0.56	2.46±0.73	0.38
PVR ($dynes \cdot s \cdot cm^{-5}$)	862±316	717±319	0.06
PaO_2 (Torr)	57.1±9.8	61.7±9.8	0.06
Central disease score	0.93±0.98	2.04±1.32	<0.0001
Intraoperative classification			
Type 1/2/3/4	13/8/4/0	18/0/0/0	
Non-type 1	48.0	0.0	0.0005
Operative mortality (%)	4.0	5.6	0.81
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	405±303	234±115	0.05
% decrease in PVR (%)	55.6±21.3	69.9±18.3	0.04

Values are mean±SD or n (%).
Abbreviations see in Tables 1,3.

Table 6 Characteristics of Female in HLA-B*5201-Positive or -Negative Type

	HLA-B*5201 positive (n=37)	HLA-B*5201 negative (n=52)	p value
Age (years)	53.9±10.5	54.2±11.6	0.90
DVT (%)	13.5	42.3	0.0036
Embolic episode (%)	27.0	40.4	0.19
Pra (mmHg)	3.9±3.7	4.6±3.3	0.25
Mean Ppa (mmHg)	43.7±11.3	45.8±10.9	0.08
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.77±0.61	2.59±0.56	0.15
PVR ($dynes \cdot s \cdot cm^{-5}$)	837±460	862±316	0.14
PaO_2 (Torr)	57.1±10.5	57.1±9.8	0.35
Central disease score	1.24±0.98	0.93±0.98	0.11
Intraoperative classification			
Type 1/2/3/4	13/1/1/0	13/8/4/0	
Non-type 1	13.3	48.0	0.02
Operative mortality (%)	0.0	4.0	0.43
Postoperative PVR ($dynes \cdot s \cdot cm^{-5}$)	365±223	405±303	0.68
% decrease in PVR (%)	53.7±25.5	55.6±21.3	0.81

Values are mean±SD or n (%).
Abbreviations see in Tables 1,3.

CTEPH based on HLA types, we compared the clinical characteristics of HLA-B*5201-positive and -negative females. As shown in Table 6, HLA-B*5201-positive females had less history of DVT (13.5 vs 42.3%, p=0.0036) and less non-type 1 disease (13.3 vs 48%, p=0.02) compared with HLA-B*5201-negative females.

Discussion

The incidence of pulmonary thromboembolism in Japan in 2004 (4,106 patients) was much lower than in the USA (630,000)[20] The absence of factor V leiden and prothrombin mutation, and low lipid levels in the Japanese might be involved in the difference between Japanese and Caucasian populations with this disease[21,22] However, female predominance and a higher incidence ratio of chronic to acute pulmonary thromboembolism in Japan as compared to those in the USA were recently reported[1–3] From an annual report in Japan, the total number of CTEPH patients in Japan was 800 in 2006[23] It was reported that the risk of recurrent venous thromboembolism was higher in men than women, but the female-to-male ratio in CTEPH is 2.1 in Japan, much higher than that of 0.7 in the USA[3,7,8] In addition, we previously reported that HLA-B*5201-positive patients with Japanese CTEPH were predominantly females and were unrelated to DVT[11] The frequency of HLA-B*5201 among the normal population in Japan was reported to be 20%, much higher than 2% in western countries[24–26] Then we considered that the HLA-B*5201-positive type indicates Japanese-specific CTEPH, and that HLA-B*5201-negative type could indicate CTEPH related to DVT, similar to Western countries.

We investigated whether the clinical phenotype in female CTEPH differs from male CTEPH, especially in the Japanese series.

Female patients were elderly and had less DVT, less acute embolic episodes, a higher cardiac index, lower mean Pra, lower PaO_2, more peripheral thrombi and less improvement through surgery than males. When the patients were divided according to HLA-B*5201 status, in HLA-B*5201-positive patients, females showed less embolic episodes, higher cardiac index and lower mean Pra with lower operative mortality. In contrast, in HLA-B*5201-negative patients, females showed less embolic episodes and more peripheral thrombi, resulting in less improvement through surgery.

This is the first report to reveal gender differences in the clinical characteristics of CTEPH, and that gender differences in the HLA-B*5201-positive type were dissimilar to those in HLA-B*5201-negative type.

Several issues need to be considered in the interpretation of these results. First, female CTEPH showed peripheral thrombi according to the central disease score and intra-operative classification. These findings were similar to those of Jamieson et al, who reported that females predominate in type 3 disease (distal segmental arteries only type)[10] When the patients were divided according to HLA-B*5201 status, only in HLA-B*5201-negative patients did females show more peripheral type than males, but in HLA-B*5201-positive patients such difference could not be observed. It remains uncertain why female CTEPH showed more of the peripheral type that in the USA as well as in HLA-B*5201-negative type in Japan. Although distal small DVT could induce peripheral type CTEPH, it is possible that peripheral pulmonary arteriopathy, similar to pulmonary arterial hypertension, in situ thrombosis might cause peripheral type CTEPH? As shown in Table 6, in females, the frequencies of non-type 1 in intra-operative classifications were significantly higher in HLA-B*5201-negative than in -positive type patients. We have already shown that the frequencies of HLA-B*5201 were higher in CTEPH with central predominant type[10] It seems that the existence of HLA-B*5201 might be related to a more proximal location of thrombi only in females.

Second, female patients showed less history of DVT. However, there was no significant difference in DVT between males and females when the patients were divided by HLA-B*5201 status. Additionally, multiple regression analysis revealed that the HLA-B*5201-positive type significantly correlated with the absence of DVT, but female gender did not show significant correlation with DVT. It is likely that a significant correlation with female gender might be related to female predominance in the HLA-B*5201-positive type. Takayasu arteritis is epidemiologically known for its female predominance, and the association of HLA-B*5201 with this disease has been well documented in Japan[13,14,27] Takayasu arteritis is a chronic vasculitis, mainly involving the aorta and its major branches, as well as the coronary and pulmonary arteries[28] The frequency of HLA-B*5201 in CTEPH was similar to that reported in Takayasu arteritis[27] We previously reported that the HLA-B*5201-positive type showed female predominance and was unrelated to DVT, and that this Japanese-specific type might include underdiagnosed pulmonary arteritis secondary to thrombi, although Takayasu arteritis was clinically excluded by CT angiographies. In our series, the frequency of HLA-B*5201-positive type (27.0%) in male CTEPH was not dissimilar to that in the normal Japanese population (20.0%), while that in female CTEPH (41.6%) was much higher. Only female CTEPH in HLA-B*5201-positive type could be a specific Japanese type unrelated to DVT, caused by underdiagnosed arteritis secondary to thrombi.

Third, univariate analysis showed that female patients had less history of acute embolic episode regardless of the existence of HLA-B*5201. The results obtained by multiple logistic regression also showed that acute embolic episode was influenced by gender more strongly than the existence of HLA-B*5201. The peripheral type of CTEPH and lower frequency of DVT might be related to less embolic episodes.

Fourth, female patients showed higher cardiac index and lower mean Pra, indicating preserved right ventricular function. Although preserved right ventricular function in females was significant only in HLA-B*5201-positive type, 2-way factorial ANOVA revealed that female gender had the main effect on higher cardiac index and lower mean Pra independent of the existence of HLA-B*5201. Several studies of the left ventricle have suggested that female gender is associated with more favorable myocardial adaptations to hemodynamic overload, including a better preserved contractile response and a greater adaptive hypertrophic reserve[29–31] Our data for the right ventricle were consistent with these data. The use of diuretics did not differ between males and females (62.5 vs 62.7%, p=0.99). Only fifteen patients had systemic hypertension, with 3 of them taking an angiotensin converting enzyme inhibitor. Therefore, it is unlikely that such medications might have strong effects on gender difference in terms of right ventricular function.

Female patients had less heart disease compared with males. After excluding patients with heart disease, females still showed higher cardiac index and lower mean Pra. In

addition, there was no significant differences in pulmonary capillary wedge pressure (7.3 vs 6.1 mmHg, p=0.83) between male and female CTEPH. Further studies on gender differences regarding right ventricular function will be needed.

Fifth, female patients showed higher postoperative PVR and a modest percentage decrease in PVR in all patients as well as in the HLA-B*5201-negative type. In contrast, the mortality of female patients was lower than that of males in only the HLA-B*5201-positive type despite similar postoperative PVR and percentage decrease in PVR. The peripheral type of emboli in females could be related to less improvement using surgery in all patients as well as in the HLA-B*5201-negative type. In contrast, it is likely that better right ventricular function in females contributes to lower mortality in HLA-B*5201-positive type. We previously reported that the female HLA-B*5201-positive type had a tendency to be the central predominant type.[1] In the present study, HLA-B*5201-positive females showed more type 1 disease compared with HLA-B*5201-negative females, although there was no significant difference in central disease score. More type 1 disease in HLA-B*5201-positive females could be related to lower mortality.

Finally, the present study is based on the results from a single institution, and the number of patients in each group subcategorized according to gender and HLA type was small. Nonetheless, it will be important to manage patients while taking into account gender differences and HLA type. Larger studies are needed to confirm the relationship of gender difference and clinical phenotype.

In conclusion, to our knowledge, this is the first study to report that clinical phenotype in female CTEPH differed from that in males, and that gender differences in HLA-B*5201-positive type were dissimilar to those in HLA-B*5201-negative type.

Acknowledgement

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Disclosure

The authors have no conflicts of interest to disclose.

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Dilatation of Bronchial Arteries Correlates With Extent of Central Disease in Patients With Chronic Thromboembolic Pulmonary Hypertension

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Background Dilatation of the bronchial arteries is a well-recognized feature in patients with chronic thromboembolic pulmonary hypertension (CTEPH). The purpose of the current study was to use computed tomography (CT) to assess the relationship between dilated bronchial arteries and the extent of thrombi, and to evaluate the predictive value of the former for surgical outcome.

Methods and Results Fifty-nine patients with CTEPH and 16 with pulmonary arterial hypertension (PAH) were retrospectively evaluated. The total cross-sectional area of bronchial arteries was measured by CT and its relationship with the central extent of thrombi or surgical outcome was assessed. The total area of the bronchial arteries in CTEPH patients was significantly larger than that in PAH patients (median [range], 6.9 [1.7–29.5] mm^2 vs 3.2 [0.8–9.4] mm^2), with the total area of bronchial arteries correlating with the central extent of thrombi. In patients who had undergone pulmonary thromboendarterectomy (PTE) (n=22), the change in PaO_2 after surgery had a tendency to correlate with the total area of the bronchial arteries.

Conclusion The total cross-sectional area of the bronchial arteries correlated with the extent of central disease in patients with CTEPH, and it might predict gas exchange improvement after PTE. (*Circ J* 2008; **72:** 1136–1141)

Key Words: Bronchial artery; Chronic thromboembolic pulmonary hypertension; Pulmonary circulation; Pulmonary embolism

In patients with chronic thromboembolic pulmonary hypertension (CTEPH), dilatation of the bronchial arteries (BAs) is a well-recognized feature on conventional angiography[1] and computed tomography (CT) angiography[2,3] As the finding of dilated BAs is rarely seen in patients with idiopathic pulmonary arterial hypertension (PAH) or acute pulmonary embolism, it has been suggested that this feature could help distinguish patients with CTEPH from those with other diseases causing pulmonary hypertension[1,3,4]

The presence of dilated BAs represents increased systemic collateral blood supply[1,2] and it plays a important role in maintaining the viability of ischemic lung parenchyma after pulmonary artery occlusion[5] However, the mechanisms of bronchial arterial development are not well understood. It is thought that both hemodynamic and nonhemodynamic factors might be involved[6] In a canine model, Rehulova et al showed that the development of collateral bronchopulmonary circulation depended on the size of the occluded branch of the pulmonary arteries[7] In patients with CTEPH, the location of thrombi varies between individuals, but to our knowledge no study has evaluated the relationship between the location of thrombi and the dilatation of BAs in humans.

Previous studies showed a lower postoperative mortality rate and lower postoperative pulmonary vascular resistance (PVR) after pulmonary thromboendarterectomy (PTE) in patients with dilated BAs according to the preoperative evaluation, compared with patients without dilated BAs[8,9] Those studies classified patients into 2 groups, with (≥1.5 mm) or without (<1.5 mm) dilated BAs. Ley et al showed a correlation between the cross-sectional area of BAs assessed by CT angiography and the bronchopulmonary shunt volume assessed by magnetic resonance imaging[2] Those results prompted us to use the cross-sectional area of the BAs, instead of their diameters, for assessment of the relationship with surgical outcome after PTE, as the bronchopulmonary shunt volume may contribute directly to supporting ischemic parenchymal tissue caused by occlusion of the pulmonary arteries.

The purpose of our study was to use CT angiography to assess the relationship between the cross-sectional area of the BAs and the central extent of thrombi, as well as to evaluate the predictive value of dilated BAs for surgical outcome.

Methods

Study Population

For this retrospective study, we searched the computer database of Chiba University Hospital to identify patients

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with CTEPH (n=74) and PAH (n=19) who had undergone CT angiography between January 2002 and August 2007. All patients, except 1 with PAH, had undergone right-heart catheterization. The diagnosis of CTEPH or PAH was made on the basis of multiple diagnostic tests, including a detailed history, physical examination, pulmonary function testing, perfusion scanning, CT scanning, echocardiogram, right-heart catheterization and serologic tests.

Fourteen patients (11 with CTEPH, 3 with PAH) were excluded because of suboptimal contrast material delivery for evaluation of the BAs. Four patients with CTEPH were also excluded because the duration between CT angiography and right-heart catheterization was more than 3 months. Finally, 59 patients with CTEPH (CTEPH group) and 16 patients with PAH (PAH group: 8 with idiopathic PAH, 4 with PAH associated with collagen vascular disease, 2 with arterial septal defect and 2 with PAH associated with portal hypertension) were evaluated. Right-heart catheterization and selective pulmonary angiography were performed in all patients of the CTEPH group.

Twenty-four patients in the CTEPH group had undergone PTE; 2 of them died in the early postoperative period, and the remainder, except 1 patient (n=21), underwent post-operative CT angiography within 3 months (median [range], 1 [1–3]) after PTE. Postoperative blood gas analyses were performed for all patients and compared with preoperative blood gas levels.

As for the control of the total area of the BAs, we evaluated 12 patients who had acute pulmonary thromboembolism (APTE), whose thrombi were treated and resolved almost completely (post-APTE group).

The Human Subject Committee of Chiba University approved the study, and written informed consent was given by all patients at the time of diagnosis.

CT Protocol

All CT scans were obtained with a 16-row multidetector CT scanner (LightSpeed Ultra16; General Electric Medical Systems, Milwaukee, WI, USA) with 1.25-mm slice thickness. Patients were injected with 100 ml of contrast material with 350 mg of iodine/ml at 3 ml/s. All CT examinations were performed for a normal workup to diagnose or evaluate CTEPH or PAH, with a scanning delay of 20–30 s for optimal pulmonary artery visualization.

Image Interpretation

CT images were reviewed by 2 investigators using a cine-mode display on a computer workstation, and final evaluations were achieved by consensus. All BAs arising from the descending aorta in each patient as depicted by CT angiography were identified. At the mediastinal window setting of the axial images, right and/or left BAs were identified as contrast material-enhanced round or curvilinear structures (Fig 1). Their diameters were measured at the most proximal site from their origin. We calculated the cross-sectional area of each BA based on its diameter, and then summed the cross-sectional areas in each patient to yield the total area of the BAs.

The CTEPH group was divided into 3 subgroups, main type, lobar type and segmental type, according to the most proximal location of thrombi observed on CT angiography. The main type (n=9) was defined as thrombi of main arteries with or without more distal thrombi location, the lobar type (n=29) was defined as thrombi of lobar arteries with or without more distal thrombi location, and the segmental type (n=21) was defined as thrombi in segmental arteries or distal location.

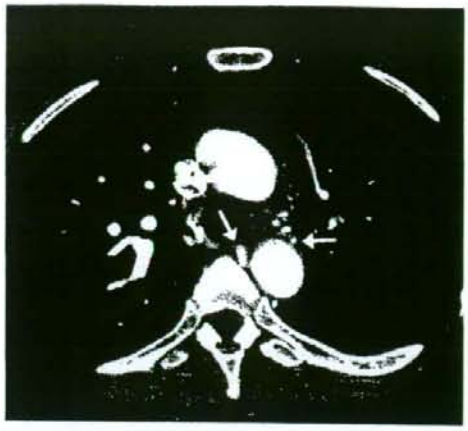

Fig 1. Computed tomography angiography in a patient with chronic thromboembolic pulmonary hypertension shows dilated bronchial arteries (arrows).

We also evaluated pulmonary infarction by the peripheral scar score as described by Heinrich et al[9]. In short, CT scan images at the lung window settings were analyzed for peripheral, irregular, wedge-shaped or linear densities. By adding up the number of involved lobes (lingual was regarded as a lobe), the peripheral scar score was obtained up to a maximum score of 6.

Statistical Analysis

Group comparisons were performed by Mann-Whitney U-test or 1-way analysis of variance on ranks (Kruskal-Wallis method) with post-hoc test using the Steel-Dwass method. When data were normally distributed with constant variance, correlations were measured using Pearson's correlation. Otherwise, the Spearman rank sum correlation was used. Comparison of the total areas of the BAs between before and after PTE was performed by Wilcoxon matched-pairs signed-ranks test. For all comparisons, a p-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Clinical and Hemodynamic Characteristics of the Patients

Table 1 summarizes the clinical and hemodynamic data from the 75 patients included in the current study. No statistical significant differences were found in terms of age, mean pulmonary artery pressure, cardiac index and PVR among the groups and subgroups.

Comparisons Between Patient Groups

The median total area of the BAs in the CTEPH group was significantly larger than that in the PAH group and the post-APTE group (Fig 2a; median [range], 6.9 [1.7–29.5] mm^2 vs 3.2 [0.8–9.4] mm^2 vs 2.0 [0.9–5.1] mm^2). When the CTEPH group was divided into 3 subgroups according to the most proximal location of thrombi, the median total area of the BAs in the segmental type was significantly smaller than in the other 2 types (Fig 2b). No significant difference in

Table 1 Clinical and Hemodynamic Characteristics of the 75 Patients in the Present Study

	PAH group (n=16)	CTEPH group				p value*
		All (n=59)	Main (n=31)	Lobar (n=18)	Segmental (n=13)	
Age (year)	50.4±16.6 (17–69)	54.9±12.2 (34–78)	60.2±9.4 (43–71)	53.7±12.6 (34–72)	54.4±12.4 (36–78)	NS
Sex (M/F)	2/14	16/43	6/3	8/21	2/19	
Mean pulmonary artery pressure (mmHg)	42.7±9.84 (26–55)	44.5±12.9 (23–71)	48.6±12.4 (32–70)	43.2±12.8 (23–71)	44.6±13.4 (23–71)	NS
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.73±0.53 (2.15–4.31)	2.56±0.63 (1.44–4.35)	2.36±0.91 (1.44–4.35)	2.46±0.54 (1.61–3.54)	2.79±0.58 (1.82–4.24)	NS
Pulmonary vascular resistance ($dynes \cdot s^{-1} \cdot cm^{-5}$)	694±202 (343–947)	828±425 (289–2,285)	986±467 (515–1,699)	839±468 (289–2,285)	746±368 (316–1,950)	NS

Data are mean ± SD (range), unless otherwise stated.
**Study groups were analyzed by Kruskal-Wallis test.*
PAH, pulmonary atrial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; NS, not significant.

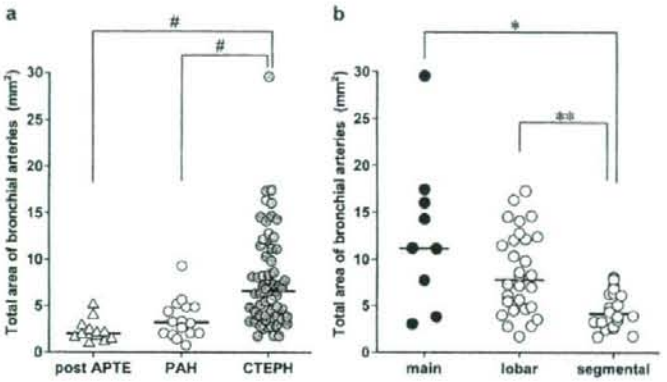

Fig 2. (a) Total area of the bronchial arteries in the post-APTE, PAH and CTEPH groups. (b) Comparison of the total area of the bronchial arteries in the 3 CTEPH subgroups according to the location of thrombi. Bars indicate median. #p<0.001, *p<0.01, **p<0.001. APTE, acute pulmonary thromboembolism; CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension.

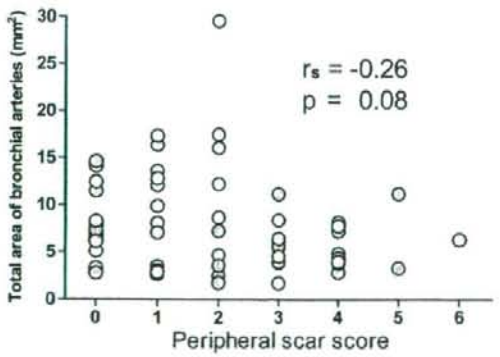

Fig 3. Correlation between peripheral scar score and total area of the bronchial arteries in the chronic thromboembolic pulmonary hypertension group.

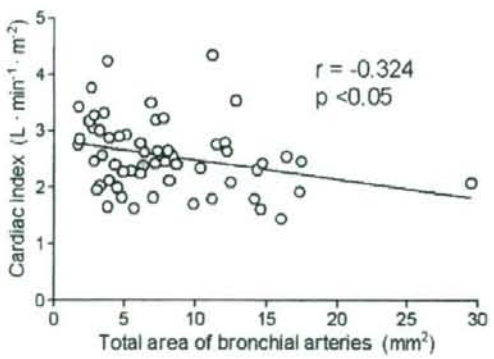

Fig 4. Correlation between the total area of the bronchial arteries and cardiac index in chronic thromboembolic pulmonary hypertension group.

total area of the BAs was observed between the PAH group and the segmental type of CTEPH. In the CTEPH group, the total area of the BAs showed a slight correlation with the peripheral scar score, but it did not reach statistical significance (Fig 3; r=–0.26, p=0.08).

Correlation With Total Area of BAs and Preoperative Hemodynamics

The total area of the BAs was significantly correlated with the preoperative cardiac index (Fig 4; r=–0.32, p<0.05). No significant correlation was found between the total area of the BAs and preoperative mean pulmonary artery pressure (r=–0.05, p=0.72) or PVR (r=0.12, p=0.37).

Table 2 Surgical Outcomes of Patients Undergoing PTE (n=22) and Correlation With Total Area of Bronchial Arteries

		Total area of bronchial arteries	
		r value	p value
Postoperative mean pulmonary artery pressure (mmHg)	26.5±12.5 (12–58)	-0.23	0.30
Postoperative cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.79±0.51 (1.85–3.63)	0.02	0.92
Postoperative pulmonary vascular resistance ($dynes \cdot s^{-1} \cdot cm^{-5}$)	388±348 (132–1,168)	-0.23	0.29
%reduction in pulmonary vascular resistance (%)	55±31 (-25–90)	0.16	0.47
Change in PaO_2 after PTE (mmHg)	14.1±13.6 (-10.9–44.3)	0.40	0.06
Change in $AaDO_2$ after PTE (mmHg)	-19.9±14.5 (-53.6–4.43)	-0.26	0.25

Data are mean±SD (range), unless otherwise stated.
PTE, pulmonary thromboendarterectomy; PaO_2, arterial oxygen tension; $AaDO_2$, alveolar-arterial oxygen pressure difference.

Correlation of Total Cross-Sectional Area of BAs With Outcome and its Change After PTE

Twenty-two patients (10 men, 12 women), mean 51.5 years (range, 18–69 years), underwent PTE and postoperative right-heart catheterization, and the relationship between the total cross-sectional area of the BAs and surgical outcome was evaluated. In this subgroup, the median total area of the BAs was 14.8 mm^2 (range, 3.6–29.5 mm^2). Every patient, except 1, had at least 1 BA with a diameter ≥1.5 mm. Based on the location of thrombi, 7 patients were classified as main type of CTEPH, 14 as lobar type, and only 1 patient was classified as the segmental type. Table 2 summarizes the surgical outcomes of the 22 patients. The total area of the BAs showed a slight correlation with changes in PaO_2, but it did not reach statistical significance (r=0.40, p=0.06). Other parameters regarding surgical outcome showed no correlation with the total area of the BAs. The total area of the BAs after PTE was significantly reduced compared with before PTE (Fig 5; median [range], 7.7 [2.3–18.9] mm^2 vs 11.2 [3.6–17.5] mm^2).

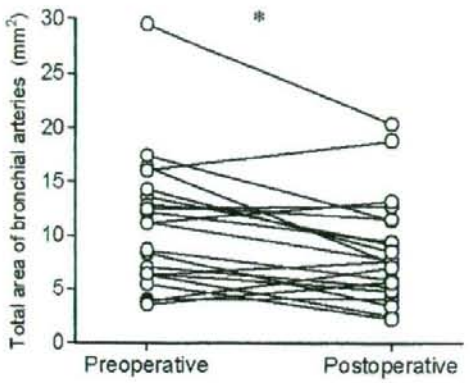

Fig 5. Comparison of the total area of the bronchial arteries before and after pulmonary thromboendarterectomy. *p<0.05.

Discussion

The current study demonstrated that the location of thrombi is related to the total cross-sectional area of the BAs in CTEPH patients. Although the BAs in the CTEPH patients were significantly dilated compared with those in the PAH patients, there was no significant difference in the total area of the BAs in the segmental type of CTEPH group and those in the PAH group. We also showed that the total area of the BAs in patients with CTEPH significantly decreased after PTE and might predict surgical outcome. With the advances in CT, the potential of CT angiography for diagnosing CTEPH has been demonstrated by a number of studies.[10–13] Moreover, CT angiography is also being recognized as a useful test for evaluating the development of systemic collateral supply to the lung.[2–4,8,9,14] Remy-Jardin et al showed that multidetector row helical CT angiography depicts the BAs more precisely than conventional angiography.[14] Therefore, in the present study we also used multidetector row helical CT angiography to evaluate the dilatation of the BAs.

Consistent with previous studies,[2–4,8,9,15] dilated BAs were frequently seen in the patients with CTEPH in the present study. The total area of the BAs in the CTEPH patients was significantly larger than that in the PAH patients. In the CTEPH group, as in earlier studies,[8,9] we did not find any significant correlation between the total area of the BAs and the preoperative mean pulmonary artery pressure or the PVR, meaning that the severity of pulmonary hypertension was not a stimulus for the development of dilated BAs. However, the total area of the BAs was negatively correlated with the cardiac index. Although the onset of CTEPH is difficult to detect, disease duration might correlate with the development of dilated BAs. On the other hand, reduction in the cardiac index occurs in the symptomatic and decompensated phase of pulmonary hypertension,[16] so disease duration might lead to this negative correlation between the total area of the BAs and cardiac index.

Of the CTEPH subgroups, the total area of the BAs in the segmental type was significantly smaller than in the other types. To our knowledge, this is the first study to investigate the correlation between BA enlargement and the central extent of thrombi in humans. The inverse relationship between the total area of the BAs and the peripheral scar score, possibly representing prior pulmonary infarction, might support this finding. One study using a dog model showed that the BAs did not become enlarged upon embolization of muscular arteries or arterioles, although enlargement occurred when the elastic branches of the pulmonary arteries were occluded.[7] This suggests that occlusion of the pulmonary arteries at the proximal sites of bronchopulmonary arterial anastomoses might open them up. In humans, preexisting bronchopulmonary arterial anastomoses are commonly seen slightly proximal to the lobular arteries.[17] The pressure gradient between the systemic arteries and the pulmonary arteries distal to the site of occlusion would increase when small distal arteries and arterioles are unaffected in patients with main or lobar type of CTEPH, and it would result in systemic arterial blood flow increasing in ischemic areas. Another possibility for the development of

systemic arterial supply to an occluded lung, related to the location of thrombi, is hyperplasia of the pulmonary artery vasa vasorum, which is of bronchial arterial origin[6,17] In addition, the extent of central disease per se may lead to nonhemodynamic factors, including pro- and anti-angiogenic factors. Our previous study showed that monocyte chemoattractant protein-1 is produced in endothelial cells, mononuclear cells, and smooth muscle cells in the fibrinous portion adjacent to the vascular lumen in endarterectomized tissue![8] Herve and Fadel speculated that macrophages infiltrating the wall of an occluded pulmonary artery stimulate proliferation of the vasa vasorum and lead to delivery of bone marrow-derived endothelial progenitor cells for local vasculogenesis within the nonresolving clots[6] Other nonhemodynamic factors that are elevated in patients with CTEPH, such as endothelin-1,[19] might play a role in development of dilated BAs.

We also showed that the total area of the BAs was significantly reduced after PTE. However, the total area of the BAs after PTE was greater compared with that in the post-APTE group. A certain number of thrombi remained after PTE, which would keep the BAs dilated. Fadel et al showed that in piglets revascularization after a period of left pulmonary artery occlusion normalized the systemic blood flow to the left lung![20] Our finding is consistent with their experimental model and we believe that reduction in the total area of the BAs after PTE can prevent hemoptysis, a life-threatening complication of CTEPH.

When we divided the CTEPH group into main type, lobar type and segmental type based on the most proximal location of thrombi, we did not find any significant difference between the total area of the BAs in the segmental type of CTEPH and that in PAH. Some previous studies have indicated that the finding of dilated BAs can help distinguish CTEPH from idiopathic PAH[3] or APTE;[4] however, those studies made no mention of the central extent of thrombi in the CTEPH patients. Although dilatation of the BAs is a common finding in CTEPH, it seems to be relatively limited to the central type of CTEPH.

Although it did not reach statistical significance ($p=0.06$), the change in PaO_2 after PTE moderately correlated with the total area of the BAs. In patients without lung disease, the bronchial circulation supplying the systemic arterial flow is estimated to be 1% of cardiac output![21] In CTEPH patients, this bronchopulmonary shunt volume can increase up to approximately 30% of cardiac output![1,2] Some animal models have confirmed that bronchial circulation supports ischemic parenchymal lung tissue![5] Besides that support, prolonged lung ischemia damages the pulmonary endothelium and leads to increasing permeability in the lung![22] In that condition, ischemic–reperfusion injury after PTE could happen to varying degrees. Development of bronchial circulation was shown to attenuate ischemic–reperfusion lung injury in some experimental models![23–25] and our data also suggest a supportive role of the BAs in the ischemic lung and their importance for gas exchange after PTE.

We did not find any other relationships between surgical outcomes, including %reduction in PVR, and the total area of the BAs. Kauczor et al found a lower postoperative mortality rate in patients with dilated BAs after PTE![8] In our study, only 2 patients died during the early postoperative period, so we did not evaluate the mortality rate. Heinrich et al reported that the postoperative PVR was significantly lower in patients with dilated BAs than in those without;[9] they classified patients into 2 groups, with (≥1.5 mm) and without (<1.5 mm) dilated BAs. In our study, as 23 of 24 patients undergoing PTE had BAs ≥1.5 mm, it is likely that we performed surgery only for the relatively central type of CTEPH and assessed only the patients with dilated BAs, and thus we could not apply their criterion for determining any correlation between postoperative PVR and bronchial arterial dilatation.

The major difference between the current study and earlier studies is that we used the total cross-sectional area of the BAs to evaluate the development of the systemic collateral supply instead of their diameters. Evaluation of bronchial arterial dilatation in CTEPH is intended for assessment of the role of systemic circulation to the lung, so a method of quantifying the systemic collateral supply would be desirable. In our study we could determine a relationship between the total cross-sectional area of the BAs and the central extent of thrombi or the increase in PaO_2 after PTE, and we believe that it is reasonable to use the total area of the BAs to assess the role of systemic circulation to the lung in patients with CTEPH.

Study Limitations

First, none of our patients underwent conventional angiography of the BAs or measurement of the bronchopulmonary shunt volume, so we could not confirm the accuracy of our findings with a "gold standard". Second, the CT protocol was optimal for pulmonary artery visualization because all CT examinations were performed for a normal workup to diagnose or evaluate CTEPH or PAH. However, we could depict the BAs sufficiently for evaluation, except for 14 cases. Third, the number of patients in each group was small. Larger studies are needed to confirm the relationship between dilated BAs and the central extent of thrombi or surgical outcomes after PTE.

In conclusion, the total cross-sectional area of the BAs correlated with the extent of central disease in patients with CTEPH and it might be useful for predicting gas exchange improvement after PTE.

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