### (3) Drug Treatment

#### 1) Initial Treatment

The major components of the treatment of acute PTE are anticoagulation therapy and thrombolytic therapy. The treatment of choice is anticoagulation therapy using unfractionated heparin.[75,76] This should be performed in all patients unless anticoagulation is contraindicated. When acute PTE is strongly suspected or a long period of time is required to confirm the diagnosis, treatment may be initiated before confirming the diagnosis. Unfractionated heparin should be administered as a single intravenous dose of 80 units/kg or 5,000 units, followed by continuous intravenous infusion at 18 units/kg/hr or 1,300 units/hr. The dose should be adjusted to maintain an activated partial thromboplastin time (APTT) of 1.5 to 2.5 times the control value (**Table 4**).[77] Infusion of unfractionated heparin should be continued until control of anticoagulation with warfarin is established.

Thrombolytic therapy is performed to promptly improve pulmonary circulation by dissolving thromboemboli, and is also used for the treatment of patients with massive acute PTE with unstable hemodynamics or echocardiography-proven enlargement of the right heart.[78] Monteplase, a recombinant tissue plasminogen activator, is the only drug officially indicated for the treatment of acute PTE in Japan.[79] The recommended regimen in adults is intravenous administration of 13,750 to 27,500 units/kg over about 2 minutes. **Table 5** lists contraindications to thrombolytic therapy.[10] Although thrombolytic therapy has been proven to be clearly superior to anticoagulation therapy in ensuring prompt dissolution of thrombi and improvement of hemodynamics,[79–83] no difference in prognosis has been observed in randomized studies of thrombolytic therapy and anticoagulation therapy.

The current criteria for drug treatment for acute PTE are as follows:

(1) Anticoagulation therapy is the treatment of choice for normotensive patients without right heart dysfunction.
(2) Normotensive patients with right heart dysfunction should be carefully assessed for expected benefits and risk of bleeding in considering whether thrombolytic therapy is a treatment option.
(3) Thrombolytic therapy is the treatment of choice for patients with persistent shock and hypotension unless it is contraindicated.

#### 2) Long-Term Treatment

Following treatment with unfractionated heparin, warfarin therapy is used. Warfarin therapy should be initiated during the early phase of treatment with unfractionated heparin, and the dose of warfarin should be adjusted to achieve an optimal prothrombin time and international normalized ratio (PT-INR). The initial dose is 3 to 5 mg in many cases. Warfarin therapy should be continued when the risk of recurrent PTE is higher than the risk of bleeding, and the duration of warfarin therapy will vary depending on the presence and types of risk factors (**Table 6**). The optimal target range of warfarin therapy is 2.0 to 3.0 PT-INR in foreign countries[84,85] but is 1.5 to 2.5 PT-INR in Japan because of the risk of bleeding.

[Levels of Recommendations]

Class I

1. During the acute phase of acute PTE, unfractionated heparin should be administered to achieve an APTT of 1.5 to 2.5 times the control value for a period of time until the effects of warfarin are stabilized.
2. Warfarin should be administered during the chronic phase of acute PTE. The duration of warfarin therapy should be 3 months for patients with reversible risk factors and at least 3 months for patients with congenital coagulopathy and those with idiopathic VTE. Warfarin should be administered for a longer period of time to patients with cancer and those with recurrent PTE.
3. In patients with persistent shock, hypotension, and unstable hemodynamics, thrombolytic therapy should be performed during the acute phase of acute PTE.

Class IIa

1. During the acute phase of acute PTE, thrombolytic therapy should be performed in normotensive patients with right heart dysfunction.

Class IIb

1. During the treatment of acute PTE, the dose of warfarin should be adjusted to achieve a PT-INR of 1.5 to 2.5.

### (4) Catheter Intervention

Catheter intervention is indicated for patients with acute massive PTE with unstable hemodynamics despite other appropriate treatment.[86,87] Catheter interventions include catheter-directed thrombolysis (CDT) and catheter fragmentation/aspiration thrombectomy.

#### 1) Catheter-Directed Thrombolysis

Use of catheters to inject thrombolytics directly to thrombus in the pulmonary arteries is not currently supported.[88] Appropriate methods of injection such as the pulse-spray technique should be used to ensure the efficacy of treatment.

#### 2) Catheter Fragmentation/Aspiration Thrombectomy

Catheter interventions other than catheter-directed thrombolytic therapy include aspiration thrombectomy, thrombus fragmentation, and rheolytic thrombectomy. These techniques are followed by thrombolytic therapy in most cases. It has been suggested that the clinical results of these techniques are comparable to that of surgical thrombectomy.[89] Efficacy evaluation should be based on improvement of hemodynamics and oxygenation, and angiographic findings should not be overemphasized.[90] Physicians should be aware that complications[91] such as injury of vascular walls, peripheral embolism, recurrent thrombosis, traumatic hemolysis, and blood loss may occur.

##### (a) Aspiration Thrombectomy

The Greenfield embolectomy device has not yet been approved in Japan. Aspiration thrombectomy using guiding catheters for percutaneous transluminal coronary angioplasty (PTCA) has attracted attention because of its simplicity and excellent clinical results.[92] On the other hand, catheters designed to percutaneously remove thrombus from the coronary arteries are not useful in the treatment of acute PTE because of their low suction power.

##### (b) Thrombus Fragmentation

Thrombus fragmentation is performed to directly break a thrombotic mass in a proximal pulmonary artery and redistribute microemboli into peripheral vessels.[93] Although the thrombi are not recovered, small fragments of a thrombotic mass will respond better to thrombolytic therapy because the total surface area exposed with thrombolytics will be increased significantly. Currently used methods of fragmentation include cutting a thrombotic mass by rotating a pigtail catheter[94] and crushing it with a balloon catheter. Hybrid

treatment techniques combining fragmentation and aspiration thrombectomy using guiding catheters have been proposed to prevent distal emboli associated with fragmentation, and have achieved excellent results.[95]

(c) Rheolytic Thrombectomy

Rheolytic thrombectomy is a theoretically safe method since thrombi are removed, but is in many cases ineffective when used alone to treat acute PTE.

[Levels of Recommendations]

1. CDT: Class IIb
   The efficacy of simple injection of a thrombolytic agent into the affected pulmonary artery does not differ from that of systemic administration of the drug.
2. Catheter fragmentation/aspiration thrombectomy: Class IIb
   Aspiration thrombectomy
   Thrombus fragmentation
   Rheolytic thrombectomy

### (5) Surgical Treatment

#### 1) Indications for Surgery

(a) Treatment Strategies for Acute PTE

When a diagnosis of acute PTE is made, anticoagulation and/or thrombolytic therapy should be promptly initiated. However, since exacerbation of acute PTE may be observed and cardiac arrest may occur during the course of thrombolytic therapy, patients should be carefully monitored and considered for surgery throughout medical treatment. Many reports have indicated that surgical treatment improves the condition of patients with unstable hemodynamics due to massive PTE, and recent surgical techniques may achieve favorable results in patients with massive PTE.[96–98] Treatment strategies for patients who develop PTE following surgery should be determined in accordance with the type of surgery and the general condition of patients.

(b) Indications for Surgical Thrombectomy

In patients with circulatory failure or shock due to acute massive PTE causing rapid occlusion of the pulmonary arterial trunk or both right and left main pulmonary arteries, prompt recanalization of the occluded pulmonary arteries is essential.[99] Surgical pulmonary thrombectomy under cardiopulmonary bypass is indicated for these patients. In patients without shock, conventional surgical pulmonary thrombectomy is indicated, among other conditions, (1) when tachycardia persists in the absence of hypotension and medical treatment is not effective; (2) when thrombus is observed in the pulmonary arterial trunk or both right and left main pulmonary arteries, and heart failure and/or respiratory failure is rapidly progressive; (3) when thrombolytic therapy is contraindicated; and (4) when free thrombus is present in the right atrium and/or ventricle.[100]

When post-surgical patients or bedridden patients experience the abrupt onset of circulatory collapse before the diagnosis of acute PTE and medical treatment is not effective, PCPS must immediately be initiated in the ward.[101] When such patients are confirmed not to have fatal cerebral complications and are diagnosed with shock due to acute PTE, pulmonary thrombectomy should be performed.

#### 2) Methods of Surgery

Surgical thrombectomy for the treatment of acute PTE involves incision of the affected pulmonary artery to remove thrombus under cardiopulmonary support.[74] When poor cardiopulmonary kinetics are observed before surgery, femoral veno-arterial cardiopulmonary support should be initiated promptly as a supportive measure. When shock develops in a patient in the ward, PCPS should be initiated before the patient is transferred to the operating room.

Following median sternotomy, cardiopulmonary support is initiated. An incision is made into the pulmonary arterial trunk and, when necessary, the right main pulmonary artery to remove thrombus. In patients with acute PTE, soft, rod-shaped, relatively fresh red thrombi may be removed. Although thrombus in peripheral arteries should also be removed whenever possible, postoperative thrombolytic therapy is effective in dissolving peripheral thrombus when most central thrombus is removed during surgery. Surgical thrombectomy may be performed during a beating heart procedure. However, when small thrombi are located in many segmental arteries or thrombi are tightly adherent to the vascular wall, thrombectomy should be performed during an arrested heart procedure.

#### 3) Results of Surgical Pulmonary Thrombectomy

Stein et al reviewed 46 reports on 1,300 cases of surgical pulmonary thrombectomy performed from 1985 to 2006, and reported that the mortality of patients undergoing pulmonary thrombectomy was 20%.[102] According to annual reports by the Japanese Association for Thoracic Surgery, a total of 539 patients with acute PTE underwent surgical pulmonary thrombectomy during the 7-year period between 2000 and 2006, and the in-hospital mortality was 21.2%. The results in Japan are similar to or better than those in foreign countries. The results are fairly good given the severe condition of patients. During the period between August 1996 and October 2006, the Japanese Society of Pulmonary Embolism Research conducted a survey in 60 institutions in Japan, and a total of 32 patients who underwent pulmonary thrombectomy for the treatment of acute PTE were registered.[103] Mean age was 57±17 years, and 21 patients (66%) were female. The initial presentation was shock in 23 patients, cardiopulmonary arrest in 3 patients, and syncope in 11 patients. Underlying conditions included trauma in 3 patients, malignant tumors in 3 patients, cerebrovascular disorder in 3 patients, heart disease in 1 patient, central line placement in 2 patients, and pregnancy in 1 patient. Acute PTE developed after surgery in 13 patients and during prolonged bed rest status in 8 patients. Seventeen patients were inpatients when PTE developed. Before surgical pulmonary thrombectomy, thrombolytic therapy was performed in 10 patients and catheter interventions for pulmonary embolus in 4 patients. Ten patients underwent PCPS before surgery. Six patients (18.8%) died in hospital, and 3 patients (30%) under PCPS died. IVC filters were used in 16 patients (50%).

[Levels of Recommendations]

1. Surgical pulmonary thrombectomy under cardiopulmonary bypass in patients with acute massive PTE with circulatory collapse: Class I
2. Surgical pulmonary thrombectomy for the treatment of acute massive PTE in patients without shock: Class IIa

### (6) Inferior Vena Cava Filters

Although the indications for and efficacy of IVC filters have yet to be fully determined and demonstrated, IVC filters have

been increasingly recognized as effective in preventing PTE and its complications.[104–106]

**1) Indications of Permanent IVC Filters**[107,108]

Class I: Among patients with VTE,
- Those who are contraindicated for anticoagulation therapy
- Those who exhibit treatment-related complications and adverse drug reactions to anticoagulation therapy
- Those with recurrent VTE during adequate anticoagulation therapy
- Those who are unable to continue anticoagulation therapy

Class IIa: Among patients with VTE,
- Those with venous thrombosis in intrapelvic veins or branches of the IVC
- Those with large free thrombi in proximal veins
- Those undergoing thrombolytic therapy or thrombectomy for the treatment of PTE
- Those with VTE with poor cardiopulmonary reserve
- Those with recurrent PTE following placement of filters
- Those with high risk of complications related to anticoagulants (such as ataxia and frequent falls)
- Those undergoing PEA for the treatment of chronic PTE

Class IIb: Among patients without VTE,
- Those with trauma associated with a high risk of VTE
- Those undergoing surgery with a high risk of VTE
- Those with other conditions associated with a high risk of VTE

Class III:
- Patients with acute PTE with neither right heart failure nor DVT who are undergoing anticoagulation therapy
- Patients with peripheral type of DVT who are undergoing anticoagulation therapy
- Contraindications:
- Patients with no access to the vena cava
- Patients without space to place a filter

*Use of a non-permanent IVC filter may be considered for patients with conditions for which an IVC filter will no longer be required after several weeks.

**2) Indications for Non-Permanent IVC**[109–111]

Class I: None

Class IIa:
- Patients indicated for the placement of a permanent IVC filter but who need the filter for only several weeks to prevent acute PTE.

Class IIb:
- Long-term placement of removable filters

Class III:
- Patients with acute PTE with neither right heart failure nor DVT who are undergoing anticoagulation therapy
- Patients with peripheral type of DVT who are receiving anticoagulation therapy

*Since permanent placement of IVC filters increases the risk of venous thrombosis, removable IVC filters should be removed whenever possible.

[Levels of Recommendations]

The indications for permanent and non-permanent IVC filters are listed as above.

## 2. Chronic Pulmonary Thromboembolism

### 1 Diagnosis

Diagnosis of idiopathic chronic PTE with PH (CTEPH) as a condition requiring treatment should be made according to the criteria for diagnosis provided by the Specific Disease Respiratory Failure Study Group of the MHLW (Table 7). CTEPH should be suspected in patients with exertional dyspnea. Patients in whom CTEPH is suspected should be identified based on the typical symptoms and clinical findings listed in Table 7. Arterial blood gas analysis should be performed not only in patients with abnormal chest X-ray findings but also in those without remarkable X-ray findings. Patients with hypoxemia associated with hypocapnia should be assessed with ECG, echocardiography, and pulmonary function tests to exclude other cardiopulmonary diseases and to confirm the presence/absence of findings of right heart overload such as right ventricular enlargement and right ventricular hypertrophy. In making the diagnosis of CTEPH, physicians should confirm that (1) pulmonary ventilation/perfusion scintigraphy has revealed maldistribution of pulmonary blood flow without abnormal ventilation distribution that has persisted for ≥6 months; or the patient exhibits at least one of the five typical findings of pulmonary artery angiography,[112] ie, (a) pouch defects (the presence of round pouch-like shadows of thrombi that have been smoothed by blood flow, (b) webs and bands (band-like stenosis with pulmonary recanalization associated with organization of thrombi, (c) intimal irregularities, (d) abrupt narrowing, and (e) complete obstruction; and (2) right heart catheterization reveals normal pulmonary artery wedge pressure and a mean pulmonary arterial pressure of ≥25 mmHg. Cardiac catheterization is useful for measurement of pulmonary vascular resistance to determine prognosis.

Although contrast CT (MSCT) has been reported to be useful in the diagnosis of CTEPH,[113] pulmonary angiography is required to assess the condition of subsegmental arteries and to determine whether surgery is indicated.[114]

### 2 Treatment

CTEPH is treated with medical and surgical therapy, and the results with current methods of PEA are excellent. Only a few reports have described catheter interventions for the treatment of CTEPH; use of them is not expected to become common in the future, if they are used at all.

#### (1) Medical Treatment

The pathophysiology of CTEPH includes PH due to occlusion of pulmonary arteries by organized thrombi, intractable right heart failure, and hypoxemia. Accordingly, surgical removal of organized thrombi (PEA) is the only radical treatment for CTEPH. However, PEA is limited to the treatment of central type of CTEPH. Patients with peripheral type of CTEPH, those with relatively mild CTEPH who do not need surgery, and those with CTEPH with persistent PH following surgery are treated with medical treatment.

In medical treatment, patients with CTEPH who are not indicated for surgery receive anticoagulants for the treatment of VTE, which is considered the cause of CTEPH, oxygen therapy for hypoxemia, pulmonary vasodilators for PH, and cardiotonics and diuretics for right heart failure, whenever necessary.

**1) Anticoagulation Therapy**

The prognosis of untreated CTEPH depends on pulmonary hemodynamics. It has been reported that even patients with mild CTEPH may exhibit exacerbation of pulmonary hemodynamics over time.[19] Such exacerbation is believed to be caused by recurrent acute PTE, and to involve mechanisms

**Table 7. Guidelines for the Diagnosis of Idiopathic Chronic Pulmonary Thromboembolism With Pulmonary Hypertension**

Chronic pulmonary thromboembolism with pulmonary hypertension is defined as the presence of chronic obstruction of pulmonary arteries due to organized thrombi and pulmonary hypertension causing severe exertional dyspnea.

**(1) Major symptoms and other clinical findings**

1) Exertional dyspnea (Hugh-Jones Grade II or more severe) or fatigability has been observed for ≥3 months.
2) Clinical symptoms typically associated with acute pulmonary thromboembolism (abrupt onset of dyspnea, chest pain, syncope, etc.) have occurred at least once.
3) Clinical symptoms (swelling in the lower limbs and pain) suspected deep vein thrombosis in the lower limbs have occurred.
4) Pulmonary bruit is auscultated over the lungs.
5) Chest auscultation reveals abnormal sounds suggestive of pulmonary hypertension (including at least one of the following four findings: (1) increase in the pulmonary component of the second heart sound, (2) a fourth heart sound, (3) noise at the pulmonary arterial orifice during the diastolic phase, and (4) noise at the tricuspid orifice during the systolic phase

**(2) Laboratory findings**

1) Arterial blood gases
   (a) Hypoxemia associated with hypocapnia ($PaCO_2$ ≤35 Torr, $PaO_2$ ≤70 Torr)
   (b) Increase in $AaDO_2$ ($AaDO_2$ ≥30 Torr)
2) Chest X-ray findings
   (a) Enlargement of pulmonary artery shadow in hilar region (protruding left second arch or enlargement of right descending pulmonary artery; maximal diameter ≥18 mm)
   (b) Enlargement of cardiac shadow (CTR ≥50%)
   (c) Local differences in pulmonary artery shadows (right vs. left lung, upper vs. lower lung)
3) ECG
   (a) Right axis deviation and pulmonary P wave
   (b) R ≥5 mm at V1 or R/S >1, or S ≥7 mm at V5 or R/S ≤1
4) Echocardiography
   (a) Right ventricular hypertrophy, enlargement of the right atrium and ventricle, and distorted left ventricular shape
   (b) Doppler echocardiography reveals patterns characteristic of pulmonary hypertension or findings of high right ventricular systolic pressure
5) Lung ventilation/perfusion scan

   Segmental defects without abnormal ventilation distribution that have persisted or are believed to have persisted for ≥6 months even after thrombolytic or anticoagulation therapy. When findings appear to have persisted, scintigraphy should be repeated 6 months later to confirm the findings.
6) Pulmonary angiography

   As changes due to chronic thrombi, at least one of five findings, including (a) pouch defects, (b) webs and bands, (c) intimal irregularities, (d) abrupt narrowing, and (e) complete obstruction, is observed.
7) Right heart catheterization
   (a) Mean pulmonary arterial pressure during the chronic stable phase is ≥25 mmHg.
   (b) Pulmonary arterial wedge pressure is normal (≤12 mmHg).

**(3) Conditions to be excluded**

The following conditions, which may cause pulmonary hypertension or abnormal pulmonary blood flow distribution, should be excluded:

1) Left-sided heart disease
2) Congenital heart disease
3) Cor pulmonale due to ventilatory impairment
4) Primary pulmonary hypertension
5) Pulmonary hypertension due to connective tissue disease
6) Aortitis syndrome
7) Congenital malformation of pulmonary vessels
8) Pulmonary hypertension due to hepatic cirrhosis
9) Pulmonary veno-occlusive disease

**(4) Criteria for diagnosis**

All of the following criteria should be met:

1) Submission of a new case
   (a) The patient should exhibit finding 1) of "Major symptoms and other clinical findings" with or without other clinical findings.
   (b) The patient should exhibit at least 2 of the four "Laboratory findings" 1) to 4), as well as abnormal findings on either 5) Lung ventilation/perfusion scan or 6) Pulmonary angiography, and abnormal findings on 7) Right heart catheterization.
   (c) All "Conditions to be excluded" should be differentiated.
2) Renewal of a registered case
   (a) The patient should exhibit finding 1) of "Major symptoms and other clinical findings" with or without other clinical findings.
   (b) The patient should exhibit "Laboratory findings" 1) with or without other laboratory findings.
   (c) All "Conditions to be excluded" should be differentiated.

$PaCO_2$, partial pressure of arterial carbon dioxide; $PaO_2$, partial pressure of arterial oxygen; $AaDO_2$, alveolar-arterial oxygen difference; CTR, cardiothoracic ratio.
Provided by the Specific Disease Respiratory Failure Study Group of the Ministry of Health, Labour and Welfare.

of formation of thrombus *in situ*. Accordingly, life-long anticoagulation therapy with warfarin is required for patients with CTEPH. Warfarin is often administered with a target INR of 1.5 to 2.5, which is also recommended for patients with acute PTE.

**2) Thrombolytic Therapy**
Patients with CTEPH may exhibit rapid progression of disease. When levels of coagulation/fibrinolytic molecular markers such as D-dimer are high during disease progression, thrombolytic therapy may yield improvement. Physicians should be aware of this possibility.

**3) Hypoxemia**
Although there is no conclusive evidence for it, oxygen therapy is expected to improve both the QOL and prognosis of patients with CTEPH. In Japan, home oxygen therapy (HOT) for patients with PH including CTEPH is covered by the NHI.

**4) Treatment of Right Heart Failure**
The presence of clinically significant right heart failure is an important determinant of the prognosis in CTEPH. Patients with right heart failure who exhibit pleural effusion, hepatomegaly/abnormal hepatic function, thrombocytopenia, leg edema, or other typical signs/symptoms are treated with conventional regimens for heart failure including bed rest, restriction of water intake, diuretics, and oral cardiotonics. Patients in severe condition also require intravenous administration of catecholamines such as dopamine and dobutamine as well as milrinone.

**5) Vasodilatation**
Although use of classic vasodilators such as calcium blockers, nitrates, and angiotensin converting enzyme (ACE) inhibitors to treat CTEPH has been attempted, the efficacy of these drugs in patients with CTEPH has not been demonstrated. However, recent studies have evaluated the effects of beraprost[35] and epoprostenol,[115] drugs indicated for pulmonary arterial hypertension, on CTEPH. Open-label studies and placebo-controlled studies of bosentan[36,116] and sildenafil[37] have revealed that these drugs may significantly improve pulmonary hemodynamics, six-minute walking distance, and brain natriuretic peptide (BNP) level, and so on. The efficacy of regimens combining these drugs has also been reported. However, use of these drugs for the treatment of CTEPH is currently not covered by NHI in Japan.

[Levels of Recommendations]
1. Anticoagulation therapy: Class IIa
2. Oxygen therapy/HOT: Class IIb
3. Vasodilatation for the treatment of PH: Class IIb
4. Cardiotonics and diuretics for right heart failure: Class IIb

### (2) Surgical Treatment

**1) PEA by Lateral Thoracotomy**
PEA is almost fully established as a method of treatment of CTEPH. Lateral thoracotomy had been used before PEA by median sternotomy with cardiopulmonary bypass and deep hypothermic intermittent circulatory arrest was established as the standard technique. The indications for PEA by lateral thoracotomy are similar to those for the method by median sternotomy, though this procedure is currently considered for only a limited number of patients.[117–123]

a) Surgery
Incision along the fourth or fifth rib is made to approach the pulmonary artery. Dissection is started from the interlobar fissure to expose the segmental arteries. Taping is performed to control back flow of blood from peripheral vessels. Dissection must be performed carefully so as not to injure the pulmonary parenchyma. After administration of heparin, either the right or left main pulmonary artery is clamped without cardiopulmonary bypass to monitor changes over time in pulmonary arterial pressure for about 5 minutes. After confirming that pulmonary arterial pressure does not exceed systemic blood pressure, an incision is made into the affected lobe artery to initiate thromboendarterectomy. The dissecting plane is determined as in the median sternotomy technique. The target organized thrombus and the intima are held and pulled along the direction to each segmental artery without cutting off the thrombus and the intima. Following removal of the thrombus and the intima, the peripheral taping is removed to confirm back flow of blood. The incision over the lobe artery is closed by suturing or using an autologous pericardial patch.

b) Results of Surgery by Masuda et al
Since 1986, Masuda et al have performed PEA by lateral thoracotomy in 16 patients. In all patients, a right lateral thoracotomy incision was used to access the pulmonary arteries. No patients exhibited serious arrhythmia or right heart failure. No patients required emergency cardiopulmonary bypass for the treatment of hypoxemia. Two patients underwent thromboendarterectomy by left lateral thoracotomy as a second-stage procedure in a two-staged operation. Two patients (12.5%) died of surgical complications, due to postoperative pneumonia and postoperative pulmonary edema in one case each. The patients who survived surgery exhibited prompt improvement in mean pulmonary arterial pressure, cardiac index, and pulmonary vascular resistance, and gradual improvement in $PaO_2$ over time, resulting in significant improvement 6 months after surgery. Three patients died 4,220, 1,891, and 1,173 days after surgery, due to sudden death in 2 patients and heart failure in 1 patient. Relationships were suspected to exist between these late-phase deaths and CTEPH.

c) Summary
Median sternotomy, which enables PEA in both right and left pulmonary arteries in one stage, is used as the standard procedure for treatment of CTEPH, and has yielded favorable results, particularly in patients with central type of CTEPH.[16,124] The lateral thoracotomy technique should be considered only for patients with predominantly unilateral disease with peripheral pulmonary lesions.

[Levels of Recommendations]
1. PEA by lateral thoracotomy: Class IIb

**2) PEA With Deep Hypothermia**

(a) Indications for Surgery
Findings of various examinations including pulmonary angiography, MSCT, pulmonary perfusion scintigraphy and right heart catheterization are important in determining treatment strategies for CTEPH. Daily et al[125,126] reported that surgical treatment of CTEPH is indicated for patients with a pulmonary vascular resistance of ≥300 dyne·sec·cm$^{-5}$ in whom pulmonary angiography reveals occlusive lesions of the lobe arteries, while Jamieson et al[28,127] described this technique as indicated for patients with (1) a mean pulmonary arterial

pressure of ≥30 mmHg and a pulmonary vascular resistance of ≥300 dyne·sec·cm$^{-5}$; (2) central edges of thrombi located in surgically accessible areas; and (3) without serious complications. Important determinants of the use of surgery for the treatment of CTEPH are the configuration of occluded pulmonary arteries and clinical manifestations (New York Heart Association [NYHA] Class III or higher without shock).[31,128,129] In terms of configuration of affected pulmonary arteries, surgery is indicated for patients with central type of CTEPH that affects central pulmonary arteries including the main pulmonary artery, interlobar arteries, and segmental arteries and causes mural thrombi and intimal hyperplasia, while effective surgical treatment may not be possible in patients with peripheral type of CTEPH affecting peripheral portions of segmental arteries and subsegmental arteries. Appropriate selection of patients is thus important.[130]

(b) Surgical Techniques

Unlike acute PTE, the thrombi in CTEPH are pale white, and organized thrombi are attached firmly to the pulmonary arterial wall. During surgical treatment of CTEPH, organized thrombi must be removed together with the intima.[129] The San Diego group including Daily et al[125] and Jamieson et al[28] developed a technique termed PEA in both lungs, which involves a median sternotomy with cardiopulmonary bypass and deep hypothermic intermittent circulatory arrest. PEA is the standard surgical technique for the treatment of CTEPH,[124,130–134] since CTEPH usually develops in both lungs; the right and left lungs can be approached simultaneously; cardiac lesions complicated by CTEPH can be treated; and the risk of pulmonary bleeding due to thoracotomy is low.

a) Important Aspects of PEA

Techniques to remove thromboemboli alone without removing the intima are completely ineffective in the treatment of CTEPH. In removing the intima, it is important first to determine the dissecting plane appropriately. Optimally, the dissecting plane should be located between the internal elastic membrane and the media. Second, since organized thrombi are hard and not fragile, the target thrombus and intima should be slowly peeled peripherally to the segmental arteries by pulling the thrombus to remove the tree-like organized thrombus with intima. Third, it is important to ensure a blood-free surgical field. Jamieson strippers are useful for this purpose, and intermittent circulatory arrest should be performed as appropriate. The duration of circulatory arrest should be ≤15 minutes each time. When venous oxygen saturation is decreased to 90%, reperfusion should be performed for at least 10 minutes before restart of circulatory arrest. Major challenges of PEA include the treatment of peripheral occlusive lesions for which surgical thromboendarterectomy cannot be performed by median sternotomy and treatment of patients with fragile mural thrombi for which traction during dissection is difficult to perform.

b) Procedures for PEA

a. Presurgical preparation: In patients with DVT and those with a history of it, an IVC filter is placed before PEA. During surgery, patients should be monitored for deep body temperature (pharyngeal temperature), arterial pressure, and pulse oximetry. Transesophageal echocardiography and Swan-Ganz catheter placement are performed. Endotracheal tubes are placed in the right and left bronchi to prepare for pulmonary bleeding, and ice bags to wrap the head are also prepared. Autologous blood recovery systems (Cell Saver) are used during surgery.
b. Following a median sternotomy, cardiopulmonary bypass is performed with venous drainage from the superior vena cava (directly) and the IVC (through the right atrium) and arterial return to the ascending aorta. When ventricular fibrillation occurs after the initiation of cooling, a left atrial vent is inserted from the right upper pulmonary vein.
c. Under hypothermia, the superior vena cava is freed completely from the right atrium to the innominate vein. The frontal surface of the right main pulmonary artery is exposed to the right superior pulmonary vein, and the left main pulmonary artery to the pericardial reflection.
d. PEA of the right pulmonary artery: A retractor is placed between the superior vena cava and the ascending aorta, and a vertical incision of the right pulmonary artery is made from level of mobilized aorta, past right upper lobe branch, and into the right lower lobe artery. On the posterior wall, a dissecting plane is developed to start PEA. In patients with thrombus in the main pulmonary artery, the dissecting plane can be identified at the site of incision. Under hypothermia to a deep body temperature of 18°C and intermittent circulatory arrest, PEA is performed distally to each segmental artery using a Jamieson stripper. Following PEA, the right pulmonary artery is closed by double running suture with monofilament material.
e. PEA of the left pulmonary artery: Using a heart net, the heart is tugged to the lower right-hand side, and the left pulmonary artery is exposed from the pulmonary trunk to the pericardial reflection. The dissecting plane is developed, and PEA is performed to each segmental artery under intermittent circulatory arrest. Following PEA, the left pulmonary arterial wall is sutured and closed.
f. When an atrial septal defect is present, it is closed. When coronary artery bypass grafting (CABG) or surgical treatment of valvular disease is required, it is performed during rewarming. Since tricuspid valve regurgitation is improved when pulmonary arterial pressure is decreased, no surgical treatment for it is required, in principle.[135]
g. Following rewarming, withdrawal from cardiopulmonary bypass is attempted. The patient can be safely withdrawn from cardiopulmonary bypass when mean pulmonary arterial pressure is 30 mmHg or less. However, when pulmonary arterial pressure is identical to systemic blood pressure or when severe bleeding from the respiratory tract is observed, PCPS is introduced before withdrawal from cardiopulmonary bypass, and protamine is administered thereafter.
h. Cardiac tamponade due to pericardial effusion may occur during the several weeks after surgery. To prevent it, pericardial fenestration is performed on the left side, and a drainage tube is inserted into the left thoracic cavity.

c) Postoperative Management

When a patient with PCPS has returned to the intensive care unit (ICU), withdrawal from PCPS is attempted over 2 to 3 days. Pulmonary edema and endotracheal bleeding due to reperfusion injury are important postoperative complications requiring careful attention.[136] When prolonged respiratory failure develops, the patient should be carefully ventilated using positive end-expiratory pressure (PEEP) for a sufficient length of time. After the risk of respiratory tract bleeding or bloody drainage is decreased, the patient should begin heparin therapy and then be switched to oral warfarin. When PH persists, long-term management of right heart failure with vasodilators (eg, prostaglandin [PG] $E_1$ and $PGI_2$) and catecholamines is required.

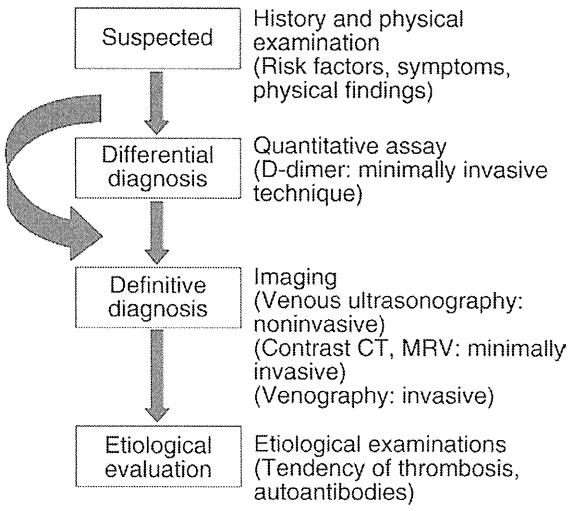


**Figure 3.** Algorithm for diagnosis of deep vein thrombosis. CT, computed tomography; MRV, magnetic resonance venography.

(c) Results of Surgical Treatment

The operative mortality of patients undergoing PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest for the treatment of CTEPH were 11.7% (12/103)[125] and 12.6% (16/127)[126] in the case series reported by Daily et al, 8.7% (13/150)[28] and 5.1% as reported by Jamieson et al,[127] 10.1% (7/69) by Tscholl et al,[137] 6% (66/1,100)[138] and 4.7% (52/1,100)[139] by Thistlethwaite et al, 5% by Bonderman et al,[140] 8.0% (7/88) by Ogino et al,[32] and 8.3% (7 out of 84 patients undergoing elective PEA) by Ando et al.[141] The results of PEA have recently improved.

Although the long-term results of medical treatment of CTEPH are not favorable, PEA is expected to improve cardiopulmonary hemodynamics and to yield a favorable long-term prognosis.[134] It has been reported that the 6-year and 5-year postoperative survival rate were 75%,[29] 86%,[32] respectively, and so on. In the patients with persistent PH following surgery, long-term results are poor.[124,131]

(d) Summary

CTEPH does not respond to medical treatment. PEA is quite effective in the treatment of central type of CTEPH. PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest, which is performed increasingly often now, significantly improves pulmonary hemodynamics and pulmonary gas exchange, and is associated with favorable results. However, patients with peripheral type of CTEPH should be carefully evaluated to determine whether this surgery is indicated for them.

[Levels of Recommendations]

1. PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest for the treatment of central type of CTEPH: Class I
2. PEA with cardiopulmonary bypass and deep hypothermic circulatory arrest for the treatment of peripheral type of CTEPH: Class IIa

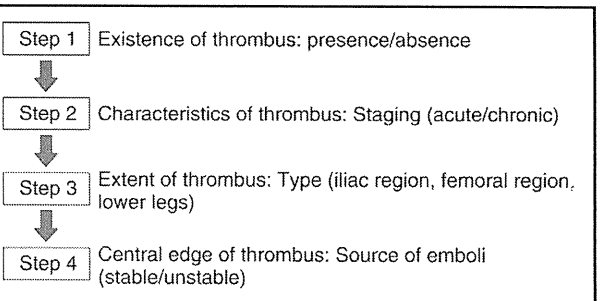


**Figure 4.** Diagnosis of deep vein thrombosis in the lower limbs by venous ultrasonography.

## 3. Deep Vein Thrombosis

### 1 Diagnosis

(1) Basic Approach

Diagnosis and treatment of DVT should always be performed considering the risk of PTE (Figures 1,2). Patients in the acute phase should be evaluated for the presence and location of thrombosis, the characteristics of possible sources of emboli, and the severity of venous insufficiency in selecting appropriate treatment strategies.[38,54,142] Figure 3 shows an algorithm for diagnosis of DVT during the acute phase.[142,143] DVT should be suspected on the basis of the history and physical examination signs/symptoms, and the presence/absence of known risk factors. Patients suspected to have acute-phase DVT[44] should be evaluated with appropriate imaging techniques that enable the presence of DVT to be promptly determined. Noninvasive venous ultrasonography is the examination of choice for evaluation of DVT in the extremities.[53,144] Minimally invasive contrast CT or magnetic resonance venography (MRV) should be performed to evaluate patients suspected to have abdominal or chest DVT.[145–147] When the presence/absence of DVT cannot be not confirmed with the above techniques, invasive contrast venography should be performed.[148] Differential diagnosis may be performed by quantitative assay. D-dimer can be used for patients in whom the possibility of acute-phase DVT is low.[149,150] Patients with abnormal D-dimer levels should be evaluated with imaging techniques to confirm the diagnosis. Physicians should be aware that the presence of normal D-dimer levels can exclude acute-phase DVT but cannot exclude chronic-phase DVT. Appropriate imaging techniques should be used to exclude thrombosis. Prior to treatment, the causes of DVT should be investigated.

(2) History and Present Illness

During the history and physical examination, physicians should look not only for the symptoms of acute-phase DVT but also those of PTE and arterial embolism.[38,54,142] Acute-phase DVT should be suspected when swelling, pain, or color change of the extremities is present. Central type of DVT should be suspected when unilateral swelling is noted. Central type of DVT is suspected in patients with femoral pain, while central or peripheral type of DVT is suspected in patients with lower leg pain. Central type of DVT is suspected when red purple skin is observed in the femoral region or lower leg. Patients with peripheral type of DVT are often asymptomatic. Physicians should suspect peripheral type of

**Table 8. Diagnosis of Acute and Chronic Deep Vein Thrombosis by Venous Ultrasonography**

| | Criteria | Acute phase | Chronic phase |
|---|---|---|---|
| Vein | Stenosis (compressibility) | Occlusion (noncompressing) | Stenosis (partial compression) |
| | Distention | Distended | Contracted |
| Clots | Floating | Free | Fixed |
| | Regression | None/moderate | Severe |
| | Consistency | Soft | Hard |
| | Surface character | Smooth | Irregular |
| | Brightness | Low/middle | High/middle |
| | Homogeneity | Homogeneous | Heterogeneous |
| Blood flow | Defect | Total | Partial |
| | Recanalization (in thrombus) | Absent | Present |
| | Collateral (in branch) | Absent | Present |

DVT when patients present with dyspnea and/or chest pain. Patients should be evaluated for common known risk factors of DVT (Table 3).

### (3) Medical Examination

Patients should be inspected visually for color change and swelling in the extremities, and the extremities should be palpated for pathological changes in the deep veins and muscles.[38,54,142] Central type of DVT should be suspected when color change or swelling is present in the extremities. The presence of palpable thrombotic veins in the groin is a direct finding of central type of DVT in the lower limbs. Stiff muscles in the lower legs are an indirect finding of central type of DVT, while tender muscles in the lower legs are a direct finding of central or peripheral type of DVT. Central type of DVT should be strongly suspected when patients exhibit skin color change and swelling as well as stiffness and/or tenderness of the lower leg muscles.[38,142] Severe central type of DVT should be strongly suspected when dermal necrosis of the lower legs as well as skin color change and swelling of the legs are present. A lower leg arterial Doppler test should then be performed to evaluate blood flow in the leg arteries. Patients in whom acute DVT recurs during the chronic phase of DVT exhibit findings of both chronic and acute DVT.

### (4) Laboratory Examinations

#### 1) Quantitative Examinations

Quantitative examinations are used for differential diagnosis of DVT on the basis of blood chemistry findings and blood flow. D-dimer is the most important item in screening for DVT. Blood flow is evaluated with ultrasonography, which can determine vessel blood flow, and plethysmography, which can determine blood flow in the lower limbs. Among ultrasonographic techniques for diagnosis of DVT, continuous wave Doppler is used to check for arterial perfusion disorder, while color Doppler and pulsed Doppler are used to check for occlusion and resumption of blood flow.[38,142] Air plethysmography is commonly used to evaluate lower limbs vein function.

#### 2) Imaging Techniques

Imaging techniques such as ultrasonography,[151] contrast CT,[152] MRV, and venography are used to confirm the morphological diagnosis of DVT. During lower limb venous ultrasonography (Figure 4), the following four steps of investigation should be performed: (1) determination of the presence/absence of thrombus in lower limb veins; (2) when thrombus is detected, evaluation of its characteristics to stage disease; (3) when acute-phase DVT is present, determination of the extent of thrombus to determine the type of DVT; and (4) examination of the central edge of the thrombus to evaluate it as a potential source of emboli. Staging should be performed based on comprehensive evaluation of noncompressing veins, brightness of thrombus, and perfusion defects, among other findings[142] (Table 8). Although venous ultrasonography is a highly reliable technique for diagnosis of acute-phase DVT, it is of limited use in the diagnosis of chronic DVT. On contrast CT, the diagnosis of DVT can be made based on findings of venous filling defects. MRV can also provide findings of thrombosis useful in the diagnosis of DVT, though its reliability is less than that of contrast CT. Since venography provides findings of venous filling defects and delineates the border of thrombus, it can be used to diagnose DVT reliably and exclude other possible diseases.[153,154]

#### 3) Etiological Evaluation

Etiological evaluation includes blood tests to check for tendency of thrombosis such as the presence of thrombophilia and autoantibodies. Coagulation/fibrinolytic markers are useful in the determination of treatment strategies and the prevention of recurrent DVT. Patients should be examined for congenital conditions such as protein S deficiency, protein C deficiency, and antithrombin deficiency as well as for acquired conditions such as decrease in levels of coagulation inhibitors and increase in levels of tissue factors. Antiphospholipid antibodies, which are autoantibodies known to be associated with DVT, should also be tested.

[Levels of Recommendations]
1. D-dimer: Class IIa
2. Venous ultrasonography: Class I
3. MRV: Class IIa
4. Contrast CT: Class I
5. Venography: Class I

## 2 Treatment

### (1) Introduction (Current Concepts)

Whether a thrombus developing in a deep vein will grow or not depends on external factors as well as the balance between the intrinsic and extrinsic coagulation systems and the fibrinolytic system surrounding the thrombus. In order to ensure effective treatment of thrombosis, physicians should understand the effects of mechanical compression of veins such as that in pregnancy/delivery and surgical treatment, effects of tissue factors such as cancer on the coagulation

system, and abnormality or deficiency of regulatory proteins such as proteins C and S and antithrombin (Class I). The optimal method of treatment of DVT involves a combination of techniques to prevent the development of PTE, eliminate or dissolve venous thrombus promptly, and prevent recurrence of thrombosis, maintain the patency of veins, and preserve the function of venous valves. Physicians must consider the clinical severity and natural course of DVT in selecting drug treatment, catheter interventions, and/or surgical thrombectomy, among other techniques (Class IIa).

### (2) Drug Treatment

Heparin and warfarin are the essential components of anticoagulation therapy for patients with DVT (Class I).[78,155,156] Since the anticoagulative effect of unfractionated heparin, which is used in Japan, varies between individuals, the effect of heparin should be monitored with APTT and blood heparin concentration. The target APTT in Europe and the United States is 1.5 to 2.5 times the control APTT.[75,157–159] This level appears appropriate in Japanese patients, as well (Class I). Following initial intravenous administration of 5,000 units of heparin, 10,000 to 15,000 units of heparin should be continuously infused over 24 hours. The dose should be adjusted according to APTT values. When bleeding complications occur, heparin treatment should be suspended or permanently discontinued. Type II heparin-induced thrombocytopenia (HIT) is a serious treatment-related complication associated with arterial thrombosis and DVT caused by immune reactions. When it is suspected, heparin therapy must be discontinued immediately (Class I). Low molecular weight heparin, which is commonly used in Europe and the United States, is not indicated for the treatment of DVT in Japan. However, the indications for low molecular weight heparin have expanded, and the prevention of VTE in patients undergoing total hip replacement, total knee replacement, surgery for hip fracture, or abdominal surgery has recently been added to them.

When warfarin is administered to patients with thrombosis, heparin and warfarin should be combined for 5 days before starting warfarin monotherapy. The dose of warfarin should be adjusted to achieve a PT-INR of 1.5 to 2.5 (target 2.0) (Class IIb). The risk of bleeding complications increases in patients with a PT-INR of ≥4. Patients with de novo DVT with no known risk factors should receive warfarin for 3 to 6 months (Class IIa), while patients with recurrent DVT or long-term risk factors such as cancer, antithrombin deficiency, or antiphospholipid antibody syndrome should receive warfarin as long as the relevant risks continue (Class IIa). Systemic thrombolytic therapy decreases the incidences of DVT and the sequelae of thrombosis (Class IIa).[160–163] Urokinase (UK) should be infused intravenously at a dose of 60,000 to 240,000 units/day on Day 1 and at tapered doses from Days 2 to 7 (Class IIa).

[Levels of Recommendations]
1. Combined use of of heparin and warfarin in the treatment of acute DVT: Class I
2. Heparin control with a target APTT of 1.5 to 2.5 times the control in the treatment of acute DVT: Class I
3. Warfarin control with a target PT-INR of 2.0 (1.5 to 2.5) times the control in the treatment of acute DVT: Class IIb
4. Systemic thrombolytic therapy in the treatment of acute DVT: Class IIa

### (3) Physical Therapy (Exercise and Compression)

During the acute phase of DVT, physicians should carefully consider clinical severity and the natural course of DVT in selecting appropriate treatment such as drug treatment, catheter interventions, and/or surgical thrombectomy, among other techniques. Patients should following surgical thrombectomy start postoperative physical therapy by wearing elastic stockings and start walking shortly after surgery. Exercise and compression may enhance improvement of swelling and pain and significantly decrease the incidence of sequelae of thrombosis (post-thrombotic syndrome) (Class I).[164–166]

When treatment of DVT is initiated after the acute phase, its main purpose should be treatment of swelling and pain, prevention of recurrent thrombosis, and prevention of occurrence or worsening of post-thrombotic syndrome.

Whether elastic stockings should be used continuously or not should be determined for individual patients based on the degree of improvement of venous function. It is preferable that elastic stockings exerting higher pressures be used continuously for patients with severe symptoms or those with poor venous function.

[Levels of Recommendations]
1. Elastic stockings: Class I

### (4) Catheter Interventions (Thrombolysis, Aspiration Thrombectomy, Stenting)

The efficacy of thrombolytic therapy often depends on the timing of treatment and the volume of thrombus. Treatment should be performed as promptly as possible to ensure its success. It is preferable that CDT be initiated during the acute phase of DVT.[167,168] In the treatment of iliofemoral venous thrombosis, it is difficult to obtain sufficient thrombolysis with CDT with a small dose of UK (240,000 units/day). Some physicians remove thrombi as soon as possible using thrombosuction catheters, and then change catheters to perform CDT.[169] Aspiration thrombectomy may be combined with CDT in some cases. Endovascular treatment using balloons and stents is expected to improve the outcome of patients who have remaining stenosis following CDT.[170,171]

Anticoagulation therapy should be performed following CDT to prevent progression or recurrence of thrombosis.

[Levels of Recommendations]
1. CDT: Class IIb
2. Aspiration thrombectomy: Class IIb
3. Venous stenting: Class IIb

### (5) Surgical Thrombectomy

Surgical thrombectomy is useful in preventing severe sequelae of thrombosis in otherwise healthy patients and venous necrosis in patients with phlegmasia cerulea dolens (Class IIa), and is indicated for lesions that are not accessible by means of catheters, lesions in which thrombus cannot be sufficiently dissolved, and patients for whom anticoagulation therapy is contraindicated.[172]

Under general anesthesia, thrombi in the common/external iliac veins are removed using Fogarty embolectomy catheters. Thrombi in peripheral regions should be removed in antegrade fashion with the milking technique and the Esmarch bandage. Some are of the opinion that an arteriovenous fistula should be created. Iliac vein compression should be treated with balloon dilatation and/or stenting. Since blood does not travel backwards when the valves of the external iliac vein are intact, and blood also travels backwards when the common iliac vein is occluded and the internal iliac vein is patent, the presence/absence of remaining thrombus must be determined with

**Table 9. Risk Classification, Incidence of Venous Thromboembolism, and Recommended Preventive Treatments**

| Risk level | Lower leg DVT (%) | Central type of DVT (%) | Symptomatic PE (%) | Fatal PE (%) | Recommended preventive treatments |
|---|---|---|---|---|---|
| Low risk | 2 | 0.4 | 0.2 | 0.002 | Early ambulation and active exercise |
| Intermediate risk | 10 to 2 | 2 to 4 | 1 to 2 | 0.1 to 0.4 | Elastic stockings or IPC |
| High risk | 20 to 40 | 4 to 8 | 2 to 4 | 0.4 to 1.0 | IPC or anticoagulation therapy* |
| Highest risk | 40 to 80 | 10 to 20 | 4 to 10 | 0.2 to 5 | (Anticoagulation therapy* plus IPC) or (Anticoagulation therapy* plus elastic stockings) |

*Patients undergoing orthopedic surgery or abdominal surgery should receive enoxaparin, fondaparinux, or low-dose unfractionated heparin, while other patients should receive low-dose unfractionated heparin. Patients at highest risk should be treated with adjusted-dose unfractionated heparin (monotherapy) or adjusted-dose warfarin (monotherapy).
Enoxaparin should be administered subcutaneously at a dose of 2,000 units twice daily. Treatment should be started 24 hours after surgery. (Note: The efficacy and safety of enoxaparin therapy for ≥15 days have not been determined in Japan.)
Fondaparinux should be administered subcutaneously at a dose of 2.5 mg (1.5 mg in patients with renal function disorder) once daily. Treatment should be started 24 hours after surgery. (Note: The efficacy and safety of fondaparinux therapy for ≥15 days in patients undergoing orthopedic surgery and ≥9 days in patients undergoing abdominal surgery have not been determined in Japan.)
DVT, deep vein thrombosis; PE, pulmonary embolism; IPC, intermittent pneumatic compression.

venography and angioscopy during surgery.[173] Following surgery, heparin should be administered for 5 days, and warfarin therapy should be initiated one day after surgery and continued for 6 months. Beginning one day after surgery, patients should wear elastic stockings and walk. When an arteriovenous fistula has been created during surgery, it should be closed 6 weeks after surgery. In order to achieve favorable results, surgery should be avoided whenever possible when ≥7 days have passed since the onset of DVT.[174] Patients with phlegmasia cerulea dolens should be treated with fasciotomy in lower legs to decompress the compartment and improve circulation. Although surgical thrombectomy has yielded favorable short- and long-term results (Class IIa), the number of patients undergoing surgical thrombectomy is small in Japan.

[Levels of Recommendations]
1. Surgical thrombectomy: Class IIb

## 4. Prevention of Pulmonary Thromboembolism/ Deep Vein Thrombosis (Venous Thromboembolism)

### 1 Evaluation of the Risk of Venous Thromboembolism and Methods of Prevention for Each Risk Level

Primary prevention of VTE is considered mainly for hospitalized patients.[156,175] The risk of VTE is classified into four levels, ie, low, intermediate, high, and highest (Table 9). Each surgical or disease risk level should be evaluated comprehensively considering additional risk factors (Table 10).

**Table 10. Strength of Additional Risk Factors for Venous Thromboembolism**

| Strength | Risk factors |
|---|---|
| Weak | Obesity<br>Estrogen therapy<br>Varicose veins in the lower limbs |
| Intermediate | Elderly<br>Prolonged bed rest<br>Congestive heart failure<br>Respiratory failure<br>Malignant disease<br>Central venous catheterization<br>Cancer chemotherapy<br>Severe infection |
| Strong | History of venous thromboembolism<br>Thrombophilia<br>Leg palsy<br>Leg fixation with plaster bandage |

Thrombophilia: Antithrombin deficiency, protein C deficiency, protein S deficiency, antiphospholipid syndrome, etc.

### 2 Methods to Prevent Venous Thromboembolism

#### (1) Walking and Active Exercise

Initiation of walking and active exercise during the early postoperative period is essential to prevent VTE. When patients are unable to become early ambulatory, leg raising, massage, and active and passive foot joint exercise should be performed.[176–178]

#### (2) Elastic Stockings

During hospitalization, patients should wear elastic stockings before and after surgery as long as the risk of VTE exists.[179] Elastic stockings are beneficial since they do not cause complications such as bleeding, are easy to use, and not expensive.

#### (3) Intermittent Pneumatic Compression

Intermittent pneumatic compression (IPC) is beneficial in high-risk patients, especially those with a high risk of bleeding.[180,181] In principle, IPC should start before or during surgery. When the presence of DVT cannot be excluded prior to initiation of IPC, physicians must obtain informed consent from patients after adequate explanation of the risk of thromboembolism, and should examine patients carefully for PTE. Patients undergoing bed rest should continue IPC all day long.[182] Even after they become ambulatory, patients should use IPC during bed rest until they are able to walk for a sufficient length of time.

#### (4) Low-Dose Unfractionated Heparin

Unfractionated heparin is administered at a dose of 5,000 units every 8 or 12 hours at least until the patient is able to walk for a sufficient length of time. Physicians should consider switching from heparin to warfarin therapy when the risk of thrombosis persists and the patient requires long-term preventive therapy. The risk of bleeding should be carefully evaluated. Heparin should be administered with special care before and after spinal or epidural anesthesia. Reduction of anticoagulant dose should also be considered during these periods.

**Table 11. Classification of Risk of Venous Thromboembolism by Type of Surgery**

| Risk level | Surgery, urology, gynecology | Orthopedic surgery | Obstetrics |
|---|---|---|---|
| Low risk | Non-major surgery in patients <60 years old<br>Major surgery in patients <40 years old | Upper limb surgery | Normal delivery |
| Intermediate risk | Non-major surgery in patients ≥60 years or those with risk factors<br>Major surgery in patients ≥40 years or those with risk factors | Upper limb surgery including bone collection from the ilium or collection of nerve/skin from the lower limbs<br>Spine surgery<br>Spine/spinal injury<br>Lower limb surgery<br>Uncomplicated leg injury distal to the femur | Caesarean section (excluding high-risk pregnancy) |
| High risk | Major cancer surgery in patients ≥40 years old | Hip replacement, total knee replacement, surgery for hip fracture (including the shaft of the femur)<br>Pelvic osteotomy (eg, Chiari osteotomy of pelvis, acetabular rotational osteotomy)<br>Leg surgery in patients with additional risk factors for VTE<br>Surgery for malignant tumors of the lower limb<br>Severe trauma (multiple trauma), pelvic fracture | Caesarean section in obese women of advanced age<br>Vaginal delivery in women with a history of VTE or thrombophilia |
| Highest risk | Major surgery with a history of VTE or thrombophilia | "High risk" surgery in patients with a history of VTE or thrombophilia | Caesarean section in women with a history of VTE or thrombophilia |

Risk level should be determined comprehensively on the basis of the risks of planned surgical procedures and conditions and additional risk factors. For example, when a patient has a strong additional risk factor, risk level should be increased by one rank. Also, when there is more than one weak additional risk factor, risk should be increased by one rank.
Additional factors that increase the risk of VTE: Thrombophilia, history of VTE, malignant disease, cancer chemotherapy, severe infection, central venous catheterization, prolonged bed rest, leg palsy, leg fixation with plaster band, hormone therapy, obesity, varicose veins, etc. (Thrombophilia include antithrombin deficiency, protein C deficiency, protein S deficiency, and antiphospholipid syndrome.)
Although there is no strict definition for it, major surgery is basically understood to include all abdominal surgeries and other surgeries that require ≥45 minutes to perform, and should be further classified comprehensively based on the anesthetic techniques, volume of bleeding, volume of transfusion, and length of surgery.
VTE, venous thromboembolism.

#### (5) Adjusted-Dose Unfractionated Heparin

Adjusted-dose unfractionated heparin is administered to maintain APTT at the upper limit of the normal range. Although this technique is complicated, even monotherapy with adjusted-dose unfractionated heparin is beneficial in highest-risk patients.[183]

#### (6) Adjusted-Dose Warfarin

Warfarin is administered to maintain PT-INR at the target level. In Japan, a PT-INR of 1.5 to 2.5 is recommended.

#### (7) Low Molecular Weight Heparin and Factor Xa Inhibitors

This technique is convenient, since preventive treatment using low molecular weight heparin and factor Xa inhibitors has stable effects without significant individual differences and these drugs can be administered subcutaneously once or twice a day without close monitoring. The incidence of adverse drug reactions such as thrombocytopenia and osteopenia is low. In Japan, enoxaparin, a low molecular weight heparin product, is officially indicated for patients following total hip replacement, total knee replacement, or surgical treatment of hip fracture as well as after abdominal surgery associated with a high risk of development of VTE.[184] In addition, fondaparinux, the factor Xa inhibitor, is officially indicated for patients following orthopedic surgery of the lower limb or abdominal surgery, which are associated with a high risk of VTE.[185]

### 3 Selection of Methods of Prevention for Patients Undergoing Surgery or Medical Treatment

Table 11 classifies the risk of VTE by type of surgery. Supplemental information is provided as follows.

#### (1) General Surgery

Although there is no strict definition for it, major surgery is basically understood to include all types of abdominal surgery and other surgeries that require ≥45 minutes to perform, and should further be classified comprehensively based on anesthetic techniques, volume of bleeding, volume of transfusion, and length of surgery.[156] Physicians should determine when anticoagulation therapy will be started based on the condition of individual patients. Preventive treatment may be initiated the evening before the surgery, immediately after initiating surgery, or after surgery, based on the risks of VTE and bleeding.

#### (2) Urological Surgery

The risk of VTE is low for transurethral surgery, intermediate for pelvic surgery other than as cancer treatment, and high for total prostatectomy and total cystectomy. Prevention of VTE in patients undergoing intra-abdominal urological procedures such as renal surgery should be performed as for patients undergoing pelvic urological procedures. Although there is no strict definition for it, the classification of major urological surgeries including transurethral procedures should be performed in the same fashion as for general surgery.

### (3) Gynecological Surgery

Patients undergoing surgery for the treatment of benign disease (laparotomy, transvaginal procedures, laparoscopic procedures) or surgery for malignant disease using techniques commonly used for the treatment of benign disease and those receiving hormone therapy are considered intermediate-risk patients, while patients undergoing radical treatment of pelvic malignant tumors should be considered high-risk patients.

### (4) Obstetric Procedures

Pregnant women who remain in bed for long periods of time due to pregnancy complications should be encouraged to perform leg exercise in bed. Pregnant women who must refrain from exercise should wear elastic stockings or use IPC. When pregnant women undergo Caesarean section following long-term bed rest, physicians should consider preoperative screening for VTE. It is preferable that pregnant women with a history of VTE or thrombophilia undergo preventive drug treatment from the first trimester.

### (5) Orthopedic Surgery

Anticoagulation therapy may be performed in patients with leg fracture for whom physical preventive treatment is not feasible and who cannot immediately undergo surgery. Based on the incidence of VTE among patients with noncomplicated leg fracture distal to the femur, the risk of VTE is considered intermediate in this patient population. Since DVT may develop immediately after hip fracture, patients should immediately undergo surgery and leave the bed early. It is uncertain whether anticoagulation therapy is appropriate in patients undergoing spine surgery and those with spine injury or spinal injury, since anticoagulation therapy may pose the risk of bleeding. No safe and effective methods of prevention are available for patients with severe trauma and those with pelvic fracture.

### (6) Neurosurgery

Patients undergoing craniotomy other than that associated with brain tumor surgery are considered at intermediate risk of VTE, and patients with brain tumor undergoing craniotomy are considered at high risk. Use of high-dose steroids appears to increase the risk. Prevention of VTE through anticoagulation therapy should be initiated after the risk of bleeding complications after surgery has been decreased to an acceptable level.

### (7) Medical Field

Physical preventive therapy should be selected for patients contraindicated for anticoagulation therapy, such as those with hemorrhagic cerebrovascular disorder. Patients with myocardial infarction, respiratory failure, severe infection, or inflammatory bowel disease should be considered at intermediate risk of VTE, while patients with palsy due to stroke and those with congestive heart failure should be considered at high risk. Patients in the ICU, who often have multiple risk factors, should undergo prevention of VTE based on individual assessment of level of risk.

### [Levels of Recommendations]

1. Early ambulation and active exercise in low-risk patients: Class I
2. Use of elastic stockings by intermediate-risk patients: Class I
3. Use of IPC in intermediate-risk patients: Class IIa
4. Combined use of IPC and anticoagulation therapy in high-risk patients: Class IIa
5. Combined use of anticoagulation therapy, IPC, anticoagulation therapy, and elastic stockings in highest-risk patients: Class IIa

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## Appendix

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原　　著

# 多項目自動血球分析装置 XE-5000 を用いた幼若血小板比率（IPF%）測定における抗凝固剤と保存温度の影響
## －抗凝固剤 CTAD と室温保存の有用性－

西山美保*1　林　悟*2　兜森　修*3　山西八郎*4
末久悦次*5　倉田義之*6　柏木浩和*7　冨山佳昭*8

# Effects of Anticoagulants and Storage Temperature on Immature Platelet Fraction % (IPF%) Values in Stored Samples Measured by the Automated Hematology Analyzer, XE-5000
## －Utility of CTAD-Anticoagulation and Room Temperature Storage－

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Measurement of reticulated platelet percentage (RP%) is thought to be a useful marker for differential diagnosis and analysis of platelet kinetics in patients with thrombocytopenic disorders. Two methods are used to detect RP; flow cytometric method and immature platelet fraction (IPF) method using automated hematology analyzers. Although IPF% measured by the automated hematology analyzers is simple and convenient, we already reported that IPF% values were highly fluctuated in stored whole blood sample with EDTA-2K at 4℃ day by day. In this study we investigated the stability of IPF% in blood samples obtained from 11 patients with chronic immune thrombocytopenic purpura (ITP) and 19 healthy volunteers using the automated hematology analyzer, XE-5000 (Sysmex) under various storage conditions. EDTA-2K, 3.13% sodium citrate, acid-citrate dextrose solution (ACD), citrate-theophylline-adenosine-dipyridamole solution (CTAD), or sodium fluoride was used as an anticoagulant. When blood samples obtained from healthy subjects were stored at 4°C, IPF% values markedly increased in a time-dependent manner by any anticoagulant examined. On the other hand, there was no significant or only slight difference in IPF% values at room temperature (RT) storage except sodium fluoride. However, in patients with ITP the elevated IPF% values fluctuated widely in EDTA-2K, sodium citrate and ACD-anticoagulated samples even at RT storage. In contrast, IPF% values in CTAD samples stored at RT were highly stable in all patients with ITP up to 4 day-storage. These results suggest that the measurement of IPF% by XE-5000 provides quite stable data up to 4 day-storage in ITP patients as well as healthy subjects under CTAD-anticoagulation and RT storage conditions.

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【Key Words】 immature platelet fraction: IPF(幼若血小板分画), chronic immune thrombocytopenic purpura: ITP(特発性血小板減少性紫斑病), anticoagulant(抗凝固剤), storage temperature(保存温度), citrate-theophylline-adenosine-dipyridamole solution(CTAD 液)

網状血小板(reticulated platelet: RP)は細胞質にRNAが残存した新生血小板と考えられており，骨髄での血小板産生能を反映する有力な指標とされている。実際，網状血小板比率(RP%)の測定は，血小板減少症，特に特発性血小板減少性紫斑病(chronic immune thrombocytopenic purpura: ITP)と再生不良性貧血(aplastic anemia: AA)との鑑別診断，血小板動態の解析，および経過モニタリングとしての有用性が報告されている[1]。また最近ではITPの診断基準試案に組み込まれるなど，益々その重要性が増している[2]。

一般的にRPは，血小板RNAを蛍光色素で染色後フローサイトメトリーにより検出するFCM法で測定されているが[3)~5)]，精度は高いものの高価な機器と煩雑な操作のため本法による測定が実施可能な施設は限られているのが現状である。そのような中，RPが含まれる大型の血小板分画を幼若血小板分画(immature platelet fraction: IPF)として簡便かつ迅速に測定できる多項目自動血球分析装置XEシリーズ(Sysmex)用ソフトが市販されており，この機種を用いた幼若血小板比率(IPF%)測定の有用性が期待されている[6)~9)]。しかし検体の採血方法および保存方法がIPF%に及ぼす影響に関して詳細に検討された報告は少ない[8)~11)]。日常臨床検査において，血球計数および形態観察には抗凝固剤としてEDTA塩を用い，翌日測定する場合は検体を4℃保存することが望ましいとされているが[12)]，我々はXE-2100を用いた検討から，EDTA検体においては，保存日数によってIPF%の大きな変動を認め，当日測定以外での評価は困難であることを報告した[9)]。Osei-Bimpongらも，EDTA採血検体を4℃で24時間保存した場合にIPF%が上昇することを報告している[10)11)]。本研究では，この問題を改善するために，検体保存の至適条件を検証すべく健常人およびITP症例検体を用いて各種抗凝固剤のIPF%に及ぼす影響をその保存温度も含め経時的に検討した。

## I. 対象および方法

### A. 対　　象

特発性血小板減少性紫斑病(ITP)11例[男2例，女9例，年齢：37～82歳(中央値56歳)，血小板数：49±24×$10^3/\mu$L(mean±SD)]，および正常対照として健常人19例[男9例，女10例，年齢：22～56歳(中央値42歳)，血小板数：247±31×$10^3/\mu$L]を対象とした。ITPの診断は旧厚生省特発性造血器障害調査研究班の診断基準[13)]および国際作業部会の診断基準[14)]に従い，血小板数が100×$10^3/\mu$L未満とした。検体採取は書面にて同意を得たのちに行った。また本研究は大阪大学医学部附属病院臨床研究倫理委員会の承認を得ている。

### B. 方　　法

#### 1. 採血および保存条件

採血はシリンジ採血を行った。抗凝固剤として，EDTA-2K(インセパックII®，SEKISUI: EDTA)，3.13%クエン酸ナトリウム(インセパックII®，SEKISUI: Na-citrate)，ACD-A液(TERUMO: ACD)，CTAD液(Vacutainer®，Becton Dickinson: CTAD)，フッ化ナトリウム(インセパックII®，SEKISUI: NaF，EDTA-2K)の5種類を用い，各々の採血管に規定量を分注した。CTADは主に生体内での血小板活性化状態を調べる検査に用いられ，クエン酸に加えて，血小板の活性化を抑制するテオフィリン，アデノシン，およびジピリダモールが添加されている[15)]。これらの検体を，採血当日を1日目として測定した後，各々2等分して室温および4℃で保存し，4日目まで測定した。

#### 2. 測　　定

IPF解析用ソフトウェアIPFmasterを搭載した多項目自動血球分析装置XE-5000(Sysmex)[16)]にて血小板数およびIPF%を測定した。

#### 3. 統計処理

平均値の有意差検定はノンパラメトリック独立多群多重比較検定法(Dunn検定)を用い，5%以下を有意と判定した。

## II. 結　　果

### A. 健常人における抗凝固剤および保存温度によるIPF%の変動

最初に健常人10例において抗凝固剤および保存温度がIPF%にどのような影響を与えるか検討した(Fig. 1, Table 1)。Fig. 1には抗凝固剤の違いと保存条件により変化するIPF%の個々の変化を図示し，更にTable 1には，その平均値と標準偏差の変化，および有意差が認められたものについては*($p<0.05$)，および**($p<0.01$)を付して示した。

抗凝固剤にEDTA，Na-citrate，ACD，CTADを使用した場合は，室温保存ではIPF%に軽度上昇傾向を認めたものの(Fig. 1上段)，EDTA，Na-citrateでは3日目まで，ACD，CTADでは4日目まで有意差は認められなかった(Table 1A)。一方，4℃保存ではIPF%の上昇は室温保存に比べ顕著であり(Fig. 1下段)，EDTA-2K，CTADでは3日目以降，Na-citrate，ACDでは2日目以降有意に上昇した(Table 1B)。また抗凝固剤にNaFを使用した場合は，室温保存，4℃保存ともに，IPF%は保存日数が増加するにつれて上昇し，3日目以降は有意差を示した($p<0.01$)。また他の抗凝固剤と異なり4℃保存よりも室温保存の方が上昇の度合いが著明であった(Fig. 1, Table 1A, B)。

### B. ITP症例における各抗凝固剤によるIPF%の変動

上記の検討結果をふまえた上でさらに検討するため，健常人は9例を追加し合計19例，および患者群としてIPF%が増加していたITP症例11例について解析した。抗凝固剤としてはNaFを除いたEDTA，Na-citrate，ACD，CTADを使用し，4日間室温保存を行い，IPF%の変動について検討を行った。

採血当日(1日目)のIPF%をFig. 2に示す。尚，Aは健常人，BはITP症例の成績を示している。健常

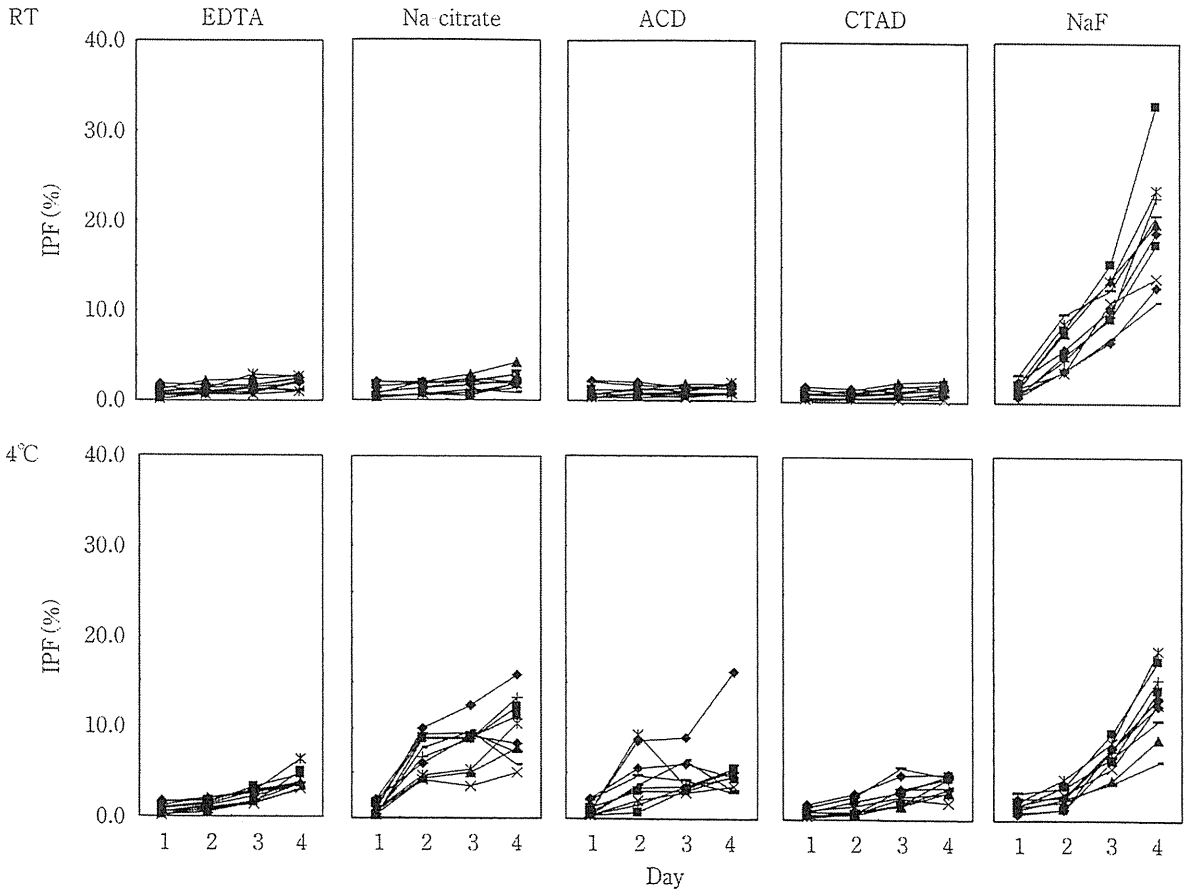


**Figure 1**　Effects of anticoagulants and storage conditions on the transition of IPF%.
Blood samples were obtained from 10 healthy volunteers with various anticoagulants (EDTA, 3.13% Na-citrate, ACD, CTAD, or NaF), and stored at room temperature (**upper** panels) or 4℃ (**lower** panels) for 4 days.　IPF% was measured by XE-5000 (Sysmex).

**Table 1** Transition of Immature Platelet Fraction (IPF) % in 10 healthy volunteers measured by XE-5000

A. Stored at room temperature

| | IPF% (mean±SD) | | | |
|---|---|---|---|---|
| Anticoagulant | Day 1 | Day 2 | Day 3 | Day 4 |
| EDTA-2K | 0.8±0.5 | 1.2±0.5 | 1.5±0.7 | 2.0±0.7** |
| Na-citrate | 0.9±0.7 | 1.3±0.6 | 1.7±0.8 | 2.2±0.9** |
| ACD | 0.9±0.7 | 1.1±0.6 | 1.1±0.5 | 1.3±0.5 |
| CTAD | 0.8±0.5 | 0.8±0.4 | 1.1±0.6 | 1.4±0.6 |
| NaF | 1.6±0.7 | 6.1±2.4 | 11.0±2.9** | 19.5±6.4** |

B. Stored at 4℃

| | IPF% (mean±SD) | | | |
|---|---|---|---|---|
| Anticoagulant | Day 1 | Day 2 | Day 3 | Day 4 |
| EDTA-2K | 0.8±0.5 | 1.3±0.5 | 2.3±0.7* | 4.1±1.0** |
| Na-citrate | 0.9±0.7 | 7.1±2.2** | 8.1±2.6** | 9.8±3.5** |
| ACD | 0.9±0.7 | 4.3±2.8** | 4.5±2.0** | 5.6±3.8** |
| CTAD | 0.8±0.5 | 1.3±0.9 | 3.0±1.4** | 3.8±1.1** |
| NaF | 1.6±0.7 | 2.6±1.1 | 7.0±1.8** | 13.2±3.8** |

Statistical comparison against IPF% of 1st days was performed with non-parametric Dunn's test.
* ; $p<0.05$ ** ; $p<0.01$ SD: standard deviation

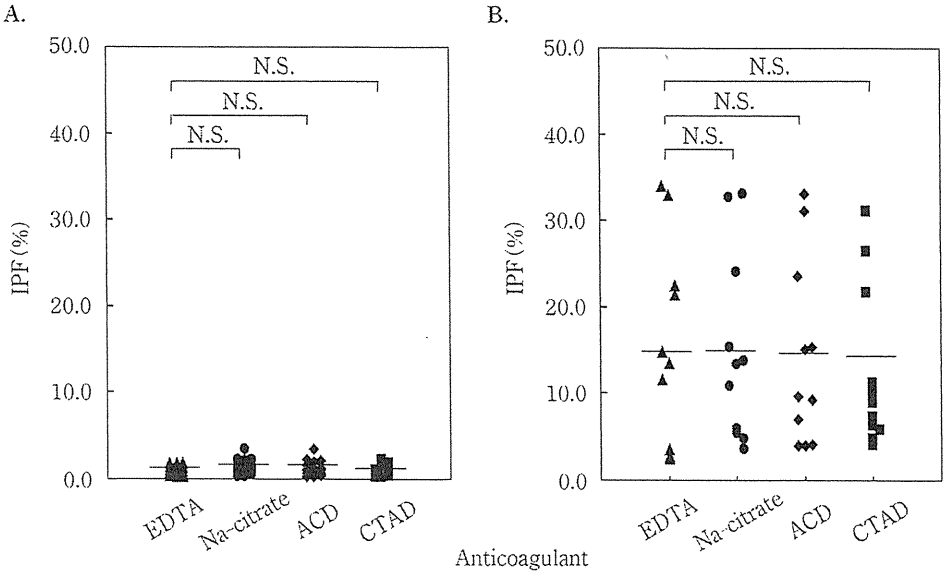


**Figure 2** IPF% in 19 healthy volunteers (**A**) and 11 patients with ITP (**B**) on day 1.
Mean values were demonstrated as horizontal bars. NS; not significant.

人 19 例の EDTA における IPF%は 0.9±0.6%であるのに対し，ITP 11 例での IPF%は 14.8±11.7%と有意に ($p<0.005$) 増加していた。また EDTA を基準として抗凝固剤間の IPF%値を比較検討したが，採血当日においては健常人のみならず ITP 症例においても有意差を認めなかった。

次に，EDTA，Na-citrate，ACD，CTAD の各抗凝固剤について測定日ごとに IPF%の平均値を求め，1 日目を基準として有意差検定を行った。**Fig. 3** の上段には各健常人のデータをプロットし，下段にはその平均値を示している。健常人 19 例においては EDTA，Na-citrate，CTAD では軽度上昇傾向を認めたものの，3 日目まで有意差を認めなかった。また ACD では 4 日目まで有意差を認めず，全ての抗凝固剤について比較的安定した値が得られた。

ITP 症例 (**Fig. 4**) においても，EDTA，Na-citrate，