

セクション分類を用いた方がよいか。

□第8版 ACCP 予防ガイドラインの目次

- ・外科手術(一般外科、血管外科、婦人科、泌尿器科、腹腔鏡手術、胸部外科、冠動脈バイパス術)
- ・整形外科手術
- ・脳神経外科手術
- ・外傷・脊椎損傷・熱傷
- ・内科患者
- ・癌患者
- ・ICU 患者

(産科、精神科は、わが国の改訂 VTE 予防ガイドライン独自の記載を予定)

ACCP に準ずる 22 名

若干修正 4 名

- ・これまでの本邦ガイドラインの記載に準ずる。
- ・脊椎手術の項の必要性を検討。

4) 長距離旅行に関して

第8版 ACCP 予防ガイドラインでは「旅行者血栓症」に関する記載されている。わが国の改訂 VTE 予防ガイドラインでは「長距離旅行」はどのように取り扱うべきか。

不要 10 名

必要 9 名

- ・社会的には必要かも知れない。
- ・災害被災者も含めた方が良いのではないか。

5) VTE スクリーニングに関して

第8版 ACCP 予防ガイドラインでは、リスクが特別に高い場合以外は、無症候例の VTE スクリーニングは推奨しないが、わが国の改訂 VTE 予防ガイドラインでは周術期・周産期の VTE のスクリーニングに関してどう考えるか。

必要なし 14 名

高リスク例のみ	6 例
必要	2 名

- ・スクリーニングの記載は混乱を招く恐れはないか。
- ・各施設の判断に任せればよい。

6) VTE 発生例に対する記載について

わが国の改訂 VTE 予防ガイドラインでは、周術期・周産期などに VTE が発見された場合の対処法に関しても記載すべきか。

参考程度に	14 名
記載	8 名
不要	4 名

- ・範囲が広すぎる。
- ・本ガイドラインの範疇ではなく、別のガイドラインなどに譲るべき。

7) 推奨のレベルを記載について

わが国の改訂 VTE 予防ガイドラインにおいて、海外のガイドラインのように VTE 予防の推奨のレベルを記載するべきか。

記載すべき	13 名
参考程度に	6 名
不要	4 名

- ・欧米と日本のエビデンスとの使い分けをどうするか。
- ・日本には治験のエビデンスしかないため、偏る可能性がある。

8) 「癌患者」「腹腔鏡手術」について

手術を受けない「癌患者」に関しては、各領域で個別に記載する方がよいか、あるいは「癌患者」の項目を作ってまとめて記載する方がよいか。また、「腹腔鏡手術」に関してはどうか。

まとめて記載	18 名
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各々のセクションで記載 4名

- ・手術をしない側からはまとめた方が分かりやすい。
- ・手術をしない患者を中心に「癌」の項目にまとめて記載したらどうか。
- ・各専門領域ならびに「癌患者」「腹腔鏡手術」項目の両方に記載したらどうか。

9) ガイドラインの公開方法に関して

わが国の改訂 VTE 予防ガイドラインは、どのような形で公開するのがよいか。

出版社	19名
学会誌	11名
WEB 公開	15名
自費出版	1名

- ・ダイジェストを各学会誌に掲載してはどうか。

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	出版年	ページ
Mashio Nakamura, Takeshi Nakano, Satoshi Ota, Norikazu Yamada, Masatoshi Miyahara, Naoki Isaka, Masaki Ito	Current Clinical Status of Venous Thromboembolism in Japan	K. Tanaka, E.W. Davie	Recent Advances in Thrombosis and Hemostasis 2008	Springer	Japan	2008	563-573

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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Current Clinical Status of Venous Thromboembolism in Japan

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Summary. Venous thromboembolism (VTE) is the third most common cardiovascular disease for which many clinical guidelines have been published in the Western world. In Japan, VTE has recently been recognized as a common disease and has received increased social as well as medical attention; however, the clinical diagnostic yield is still low. The most effective means of reducing unexpected death from VTE is to implement a comprehensive institutional policy of primary prophylaxis in patients at risk. Although it is difficult to prepare Japanese guidelines for prophylaxis of VTE based on reliable evidence, epidemiological information is available in the general surgical, orthopedic, and gynecological areas of practice. Finally, the first Japanese guidelines for prophylaxis of VTE were published in the spring of 2004. In addition, the diagnostic and management strategies have changed along with improvement in modalities and coverage by thrombolytic agents. The next goal is to gather evidence that provides the foundation for guidelines on treatment and prophylaxis. Large-scale research studies similar to those performed in the West should be conducted to elucidate the pathological mechanisms of VTE and improve its management.

Key words. Anticoagulation therapy · Prophylaxis · Thrombolytic therapy · Vena cava filters · Venous thromboembolism

Introduction

Venous thromboembolism (VTE), manifesting as either deep vein thrombosis (DVT) or pulmonary thromboembolism (PTE), is an extremely common medical problem in the Western world, occurring either in isolation or as a complication of other diseases or procedures. Many clinical guidelines for VTE have been published, such as "Guidelines on diagnosis and management of acute pulmonary embolism" (2000) by the European Society of Cardiology [1]; "Guidelines for the management of suspected acute pulmonary embolism" (2003) by the British Thoracic Society [2]; "Prevention of venous thromboembolism" (2004) by the American College of Chest Physicians [(3)]; and "Prevention and treatment of venous thromboembolism" (2006) by the Internal Union of Angiology [4]. At the same time, the incidence of VTE in Japan was considered to be minimal, and it was not a focus of attention in most Japanese medical

societies. Nonetheless, a few researchers suspected that VTE might be common in Japan and could be responsible for some unexplained sudden deaths. The lower diagnostic yield of VTE in Japan was also thought to be a contributor because the disorder is observed in multiple medical areas, including cardiovascular and respiratory medicine and surgery, and information on these cases was not disseminated systematically.

The Japanese Society of Pulmonary Embolism Research was established in 1994 [5], and international symposiums on pulmonary embolism in Japan took place in Mie in 1998 [6] and in Chiba and Sendai in 2003 and 2000, respectively [7]. These efforts were aimed at raising awareness of VTE and compiling data on Japanese cases. As a result, awareness in the medical profession has improved, diagnostic techniques have advanced, and the number of cases of VTE reported in Japan has increased rapidly. Furthermore, because of the increase in venous thromboembolic risk factors, such as continuing westernization of Japanese life and social aging, and of postoperative sudden death and travelers' thrombosis (so-called economy-class syndrome), as well as the high incidence of VTE noted following the recent mid-Niigata Prefecture earthquake, it has recently received a lot of attention, both medically and socially. In 2004, Japanese guidelines for VTE [8, 9] were published, and the increasing awareness of this disorder in Japan is changing the perception of VTE from that of a rare disease to a common one. However, large-scale studies that would help provide evidence of VTE have not been conducted in Japan. Moreover, Japan lags behind Western countries in clinical management of this disease.

Incidence and Prognosis of Venous Thromboembolism

Although VTE is diagnosed and treated in as many as 260 000 patients in the United States each year, it is estimated that more than half the cases that actually occur are never diagnosed. Thus, the true incidence may be as high as 600 000 cases [10, 11]. At the same time, the incidence of PTE in serial autopsy cases in Japan and the United States was reported as 0.8% and 23.8%, respectively, according to a previous international collaboration [12]. Moreover, the annual reports of the pathological autopsy cases in Japan noted a rate of 1.41%–1.72% [13, 14]. These results indicated that the incidence of VTE was extremely low in Japan. However, more recent reports have indicated that the incidence of DVT after joint replacement in Japan is the same as in Western countries [15, 16], and the incidence of PTE in serial autopsy cases ranged from 11% to 24% [17–20]. Consequently, the incidence of VTE in Japan is no longer considered low. Despite this evidence, data compiled from recent questionnaire surveys showed that the number of clinically diagnosed cases of PTE in Japan was only 28–32 per 1 million people [21, 22], which is 1/15th that of Western countries. We must therefore conclude that Japanese clinicians are still not entirely familiar with VTE.

Racial and environmental factors may contribute to the differences in incidence reported among Japanese and Westerners. Reports that show a higher incidence of PTE in black Americans than in black Africans [23] and no differences between white and nonwhite South Africans [24] suggest that an environmental factor is involved in

the incidence of PTE. On the other hand, the factor V Leiden mutation with activated protein C resistance, which has drawn attention as a new coagulation abnormality, is a high-frequency gene mutant that appears in 30%–50% of Caucasians with VTE [25]. No Japanese patients were found with this mutation. Similarly, no Japanese patient has the prothrombin G20210A mutation, which is associated with VTE in Caucasians [26, 27]. These findings suggest that a racial factor is also involved in the incidence of PTE. Studies among races in the United States also show that the incidence of VTE among Asians is one-fifth to one-quarter that of whites [28, 29]. Meanwhile, in our study that investigates coagulopathy in detail, only 5 of 61 consecutive patients (8%) with PTE did not have an inherited coagulopathy or a secondary risk factor for VTE [30]. These results suggest that Japanese patients might have unknown inherited coagulopathies.

In the United States, widespread prevention of VTE in hospitals led to a significant decline in the incidence of PTE beginning during the mid-1980s, although the incidence had been increasing before that period [31]. On the other hand, deaths from PTE in Japan were projected to increase by 10 times over the 50 years from 1951 to 2000 according to the vital statistics of the Ministry of Health, Labor, and Welfare [32]. The PTE rate in autopsy cases from the annual reports of the pathological autopsy cases in Japan also increased 3.5-fold from 1958 to 1997 [13, 14, 33]. These increases in PTE reflect both an "increase in appearance" and a "true increase." The "increase in appearance" indicates improved accuracy of diagnosis, such as the rising awareness among health care professionals, increasing visibility of VTE, and advances in modalities. The recent rapid increase in the incidence of this disease stems largely from these factors, which has resulted from educational campaigns in various quarters. Among the factors contributing to the "true increase" of VTE are, first, the aging of the Japanese population, which itself confers a risk of VTE; and the elderly are likely to have other risks for VTE. The second factor is change in life style. In recent decades, eating habits in Japan have become westernized, and the percentage of the population that is overweight is growing. Although the relation between VTE and metabolic syndrome is unknown, it should be considered. The third factor is advances in medical care. The risk of VTE at an inpatient setup rises according to the complexity of treatment, and the number of patients at risk further increases because the prognosis has improved for conditions such as malignancy that increase the risk of VTE. In addition, many medicines, such as oral contraceptives and drugs used in hormone replacement therapy, may increase the risk of VTE (Fig. 1).

From the point of view of prognosis, the hospital mortality rate was 14% for 309 patients diagnosed with PTE from 1994 to 1997 according to a collaborative study conducted by the Japanese Society of Pulmonary Embolism Research [34]. Among those who died, mortality among patients with shock at presentation was 30%, and it was 20% except for cases diagnosed by an autopsy, and 6% for those who presented without shock. In addition, the mortality after discharge was 3%. These results indicate that patients with PTE who are correctly diagnosed have a relatively good prognosis. However, in the following decade, the prognosis of severe cases did not improve [35] (Table 1). In addition to underdiagnosis of PTE, the high frequency of sudden death, which afflicts 25% of severe cases, and death due to recurrent PTE affect the mortality rates [36] (Fig. 2). In particular, many patients with unexpected circulatory

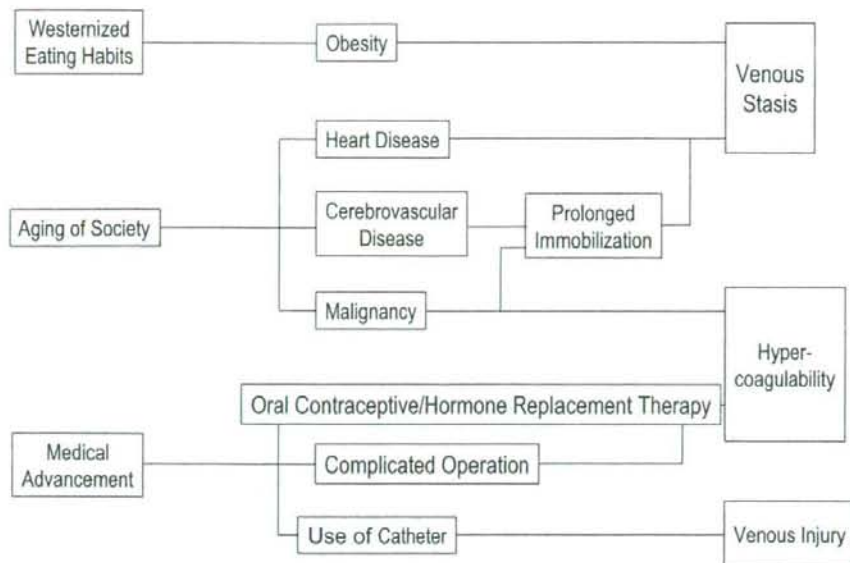


FIG. 1. Change in social structure and increasing risk of pulmonary thromboembolism

TABLE 1. Change in the mortality rate of pulmonary thromboembolism in Japan

Subjects	Change in mortality (%)		
	1/1994–10/1997 (n = 309)	11/1997–10/2000 (n = 257)	11/2000–8/2003 (n = 461)
Total	14	12	8
Cases with arrest or shock	30	32	27
Other mild cases	6	3	2

Data are from Sakuma et al. [35]

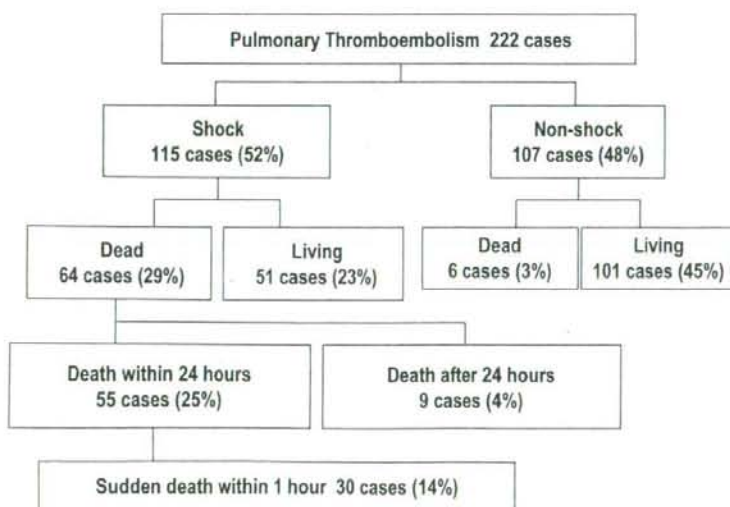


FIG. 2. In-hospital mortality of 222 patients with pulmonary thromboembolism. Sudden deaths within 1 h from onset account for 43% of total deaths with pulmonary thromboembolism

arrest succumb even with percutaneous cardiopulmonary support. Consequently, it is important to prevent PTE.

Development of Diagnostic Methods and Management of Pulmonary Thromboembolism

Many guidelines on the diagnosis and management of PTE have been published and reported at Western scientific meetings. Guidelines for the diagnosis and management of PTE have also been developed by the Japanese Society of Circulation in cooperation with other societies in Japan [9] (Fig. 3). Application of Western guidelines for PTE in Japan, as for other disorders, was uncertain because of unknown differences in the incidence of PTE in Caucasian and Japanese populations and the differences in medical care among countries. In addition, guidelines for diagnosis that are based on the situation in each country are necessary because of differences in the development of diagnostic modalities and cost.

Traditionally, the gold standard for diagnosis of PTE has been pulmonary angiography. However, efforts have been made to restrict the indications for use of pulmonary angiography, which is invasive; currently, the diagnosis of PTE tends to rely on noninvasive modalities [34, 35, 37] (Table 2). Although the main noninvasive diagnostic modality for PTE in Western countries is the perfusion lung scan, contrast-enhanced multislice computed tomography (CT) is useful in Japan. Current machines can evaluate a thromboembolism even in segmental arteries except in patients who cannot hold their breath for the necessary imaging interval. Multislice CT has the additional

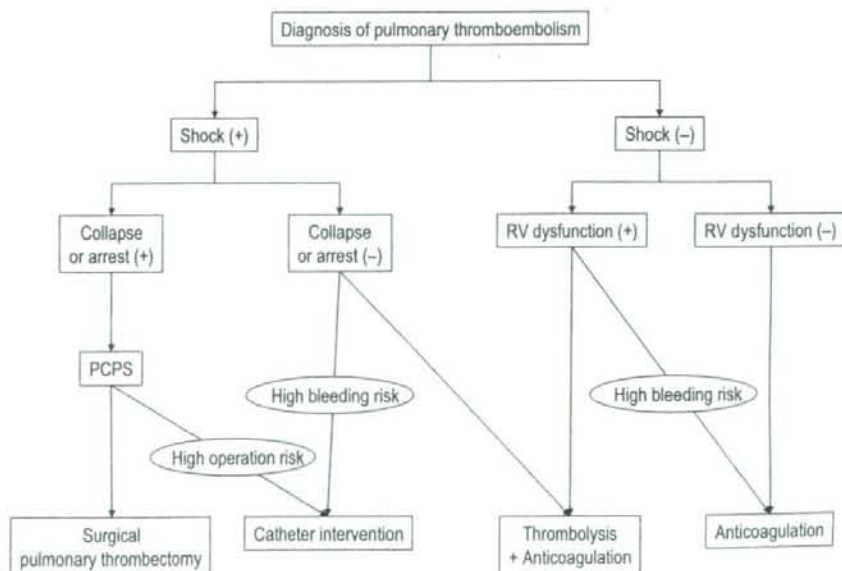


FIG. 3. Management strategy in pulmonary thromboembolism. PCPS, percutaneous cardiopulmonary support; RV, right ventricle

TABLE 2. Development of diagnostic methods of pulmonary thromboembolism in Japan

Diagnostic methods	Development of methods (%)		
	1/1994-10/1997 (n = 309)	11/1997-10/2000 (n = 257)	11/2000-8/2003 (n = 461)
Perfusion lung scan	74	77	62
Pulmonary angiography	45	57	37
Contrast-enhanced CT	14	58	62
MRI	2	6	2

Data are from Nakamura et al. [34] and Sakuma et al. [35, 37] CT, computed tomography; MRI, magnetic resonance imaging

TABLE 3. Development of diagnostic methods for DVT after the occurrence of pulmonary thromboembolism in Japan

Diagnostic method	Development (%)		
	1/1994-10/1997 (n = 309)	11/1997-10/2000 (n = 257)	11/2000-8/2003 (n = 461)
Operation rate of examination for DVT	61	65	83
Venous ultrasonography	18	24	55
Venography	81	73	41
Radio nuclear angiography	13	12	2

Operation rate indicates the ratio of patients examined for operation during each interval to the total number of patients diagnosed with DVT during that interval.

DVT, deep vein thrombosis

Data are from Nakamura [34] and Sakuma [35, 37]

advantage of being able to examine veins in the abdomen, pelvis, and legs after scanning the pulmonary arteries. The efficacy of multislice CT in PTE has been examined, and this modality is now included in the diagnostic algorithm for PTE. In addition, because of the importance of diagnosing DVT as a source of thromboembolism, venous ultrasonography, which is convenient and can be used noninvasively at the bedside, is recommended. Implementation of this modality has nevertheless been inadequate [34, 35, 37] (Table 3), and it is important to train sonographers and physicians to perform venous ultrasonography.

In the West, management guidelines for anticoagulation and thrombolysis based on a wealth of evidence are being released. No clinical trials are planned or underway to gather such evidence in Japan [38]. With regard to thrombolytic agents, which are used commonly for PTE, Alteplase, mutant tissue plasminogen activator (t-PA), has been permitted for use in patients by the Japanese government only since autumn 2005. At the same time, the effect of thrombolysis on the prognosis of patients with PTE is not clear, even in Western countries [39]. In many randomized controlled trials for PTE therapy, although thrombolysis has been shown to bring about more rapid thrombolytic and hemodynamic effects than anticoagulation, there have been no

reports that thrombolysis reduces PTE-related mortality. Therefore, the ability of thrombolysis to improve the prognosis is unknown, and its indications have not been sufficiently established. In addition, it is arguable whether thrombolysis has an effect on prognosis in severe cases. Recently, right ventricular dysfunction was identified as an important factor linked to prognosis. In the most recent randomized controlled trial of PTE in normotensive patients with right ventricular dysfunction, t-PA was found to improve the clinical course and prevent clinical deterioration; it requires an escalation of treatment compared with heparin, although the differences in mortality were not significant [40]. Therefore, thrombolytic therapy might be recommended for PTE patients with right ventricular dysfunction; however, the choice of this therapy has little scientific basis and needs further research.

Over the past few years, the use of catheter intervention for various kinds of vascular diseases has progressed, and catheter thrombolysis and catheter fragmentation are now used in patients with VTE. These techniques are being used to dissolve a thromboembolus and reduce right ventricular overload in PTE, rapidly restore a venous valve, and decrease the frequency of postthrombotic syndrome. Although it is often difficult to dissolve an obstructive DVT using conventional pharmacotherapy, a recent Japanese study reported that catheter-directed thrombolysis achieves a high dissolution rate of DVT and a reduction in the incidence of postthrombotic syndrome [41]. Thus, this technique appears to be promising.

The development of inferior vena cava (IVC) filters constitute a marked advance in the prevention of primary and recurrent PTE with DVT. When the technique was initially introduced, only permanent filters were used, and the recurrence rate of PTE after IVC filter implantation was reported to be 2% [42]. However, results of a French prospective multicenter study indicated that the long-term prognosis was worse after IVC filter implantation than after anticoagulation [43]. As a result, prophylactic use of permanent IVC filters for stable patients is not recommended. On the other hand, when anticoagulation alone is performed as PTE management, it may lead to massive recurrent PTE, a critical complication. To avoid such cases of recurrent, severe PTE, nonpermanent IVC filters have recently come into use. These filters are implanted only during the acute phase when a venous thrombus can easily migrate and the pulmonary vascular bed is small. The filter can then be removed after thrombus dissolution, decreasing the risk of embolism. Temporary IVC filters [44] and retrievable IVC filters [45] can now be used as nonpermanent IVC filters. Although temporary filters carry a risk of infection and bleeding, because they are joined to an external catheter they fare better in younger subjects and women of child-bearing age because they can be readily removed. At the same time, retrievable IVC filters are implanted as permanent filters and can be retrieved with a catheter after use. They impose fewer limitations of patient activities, and the risk of infection and bleeding is small. Moreover, they can be implanted permanently. Although the indications for use of these IVC filters have not yet been determined, the decision to use these devices should be based on the severity of the right ventricular overload and the size and ease of migration of the DVT. The trend in Japan, more so than in the West, is toward increased use of IVC filters. Once the utility of anticoagulation has been confirmed, indications for use of IVC filters should be determined carefully, especially when considering the use of permanent IVC filters (Table 4).

TABLE 4. Development of methods of management of pulmonary thromboembolism in Japan

Methods of management	Development (%)		
	1/1994–10/1997 (n = 309)	11/1997–10/2000 (n = 257)	11/2000–8/2003 (n = 461)
Anticoagulation	74	82	92
Thrombolytic therapy	50	48	58
Catheter intervention	6	6	10
Surgical pulmonary thrombectomy	2	3	2
Vena cava filter	18	34	35

Data are from Nakamura [34] and Sakuma [35, 37]

Current Status of Prophylaxis of Venous Thromboembolism

In-hospital prophylaxis of VTE is important for the following reasons: (1) the incidence of VTE is remarkably high in hospitals; (2) early diagnosis of DVT is difficult because it produces few symptoms; (3) PTE has a high fatality rate; and (4) prophylaxis of VTE is cost-efficient. Many Western medical societies have developed guidelines for the prevention of VTE based on extensive evidence. Sudden death from PTE after surgery and in other conditions is an increasing problem in Japan, and medical malpractice litigation is becoming more frequent when an appropriate treatment for PTE has not been provided. Until now, it was difficult to estimate the incidence of PTE accurately because of the difficulty of its diagnosis. However, adequate diagnosis and management of PTE is currently regarded as a matter of course, and an inadequate response by health care providers could be judged a lack of due diligence. For these reasons, a guideline for prophylaxis of VTE was anxiously awaited in Japan. As previously noted, it was impossible to use Western guidelines without modification because of differences in the incidence and use of prophylactic agents between Japan and the West. In response to this situation, the "Japanese Guideline for Prevention of Venous Thromboembolism" [8] was published in the spring of 2004 by the Editorial Committee organized by the Japanese Society of Anesthesiologists, Japanese Society of Phlebology, Japanese Society of Pulmonary Embolism Research, Japan Society of Obstetrics and Gynecology, Japanese College of Cardiology, Japanese Orthopaedic Association, Japanese Society of Intensive Care Medicine, Japanese Society of Thrombosis and Homeostasis, Japanese Urological Association, and Japan Society of Obstetrical Gynecological and Neonatal Hematology. Because few clinical studies are available that provide evidence specific to Japanese patients, the guideline remains incomplete. Even so, the participation of numerous medical societies in the development of the Japanese guideline is a significant step that is unprecedented elsewhere in the world. At about the same time, a PTE prophylaxis management fee was listed in the revised health insurance as a part of medical treatment fees in the spring of 2004. As a result, in-hospital VTE prophylaxis is starting to be implemented in many institutions. In the future, collection

of objective information from Japanese patients is urgently needed, and approval to use new anticoagulants is eagerly awaited. Fondaparinux, an anti-Xa agent, and enoxaparin, a low molecular weight heparin, became available for use in Japan in the spring of 2007 and 2008, respectively. It is expected that in the near future pharmaceutical prophylaxis with new anticoagulants will become mainstream [46, 47].

Future Outlook

The most significant development in research and practice relating to VTE is that it has been recognized as a more common disease than was previously considered. However, it is still difficult to diagnose VTE unless suspected, although diagnostic modalities are improving. A diagnostic device that can be used at the bedside to easily identify VTE is needed. The management and prophylaxis of VTE will move forward with the development of new agents. Antithrombotic agents with a lower risk of bleeding are needed because VTE is a condition that is associated with easy bleeding. The quality of diagnosis and treatment in Japan has reached Western standards. The next goal is to gather evidence that provides the foundation for guidelines of treatment and prophylaxis. Full-scale research studies such as those performed in the West should be carried out to elucidate the pathological mechanism of VTE and improve its management.

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

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

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

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

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

Pulmonary thromboembolism (PTE) is an extremely serious condition with a mortality rate of 18–30% if left untreated. It has long been the leading cause of maternal mortalities in the West,^{1–4} although considered to be uncommon in Japan. However, the incidence of PTE has been increasing in recent years as Japanese eating habits have become more similar to the West. In a 1999 patient survey, the Ministry of Health, Labor and Welfare in Japan reported 4,000 patients with PTE and 1,738 deaths from PTE, representing a 3-fold increase per decade.⁵ The annual age-adjusted PTE mortality rates markedly increased in both sexes in every decade. Finally in the 1980s, women exceeded men in age-adjusted deaths and mortality rates.⁵ According to the analysis of 309 cases of acute PTE by the Japanese Society of Pulmonary Embolism Research, the main risk factors were considered to be recent major surgery, cancer, prolonged immobilization, and obesity.⁶ Among 110 cases of recent major surgery, PTE occurred in association with orthopedic surgery (29.1%), general surgery (21.8%), gynecological surgery (18.2%), and others. More-

over, in-hospital mortality rate was 14%. Furthermore, according to maternal and child health statistics in Japan, the maternal mortality rate attributed to obstetrical PTE was 23.5% in 1995 and 22.4% in 2001, making PTE the leading cause of direct obstetrical deaths.⁷ However, no extensive surveillances of PTE in the field of obstetrics and gynecology have been conducted in Japan.

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

Methods

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

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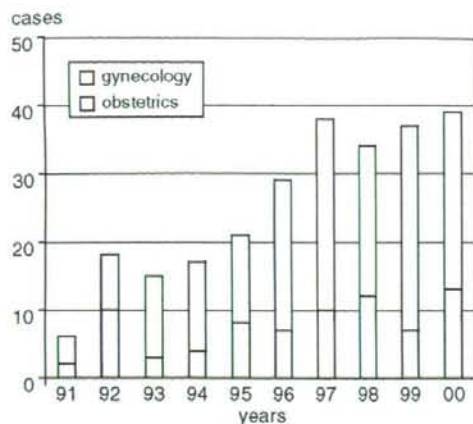


Fig 1. Number of pulmonary thromboembolism cases in obstetrical and gynecological patients.

Results

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

Fig 2 shows the different onset periods of obstetrical PTE

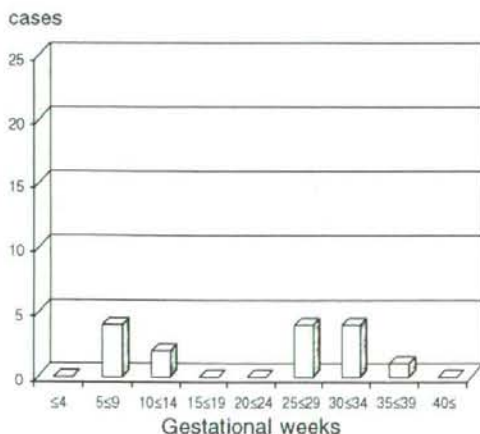


Table 1 Incidence of Pulmonary Thromboembolism Cases

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

Analysis of personal data among 254 pulmonary thromboembolism cases.

Table 2 Univariate Analysis of Pulmonary Thromboembolism Cases

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

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

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

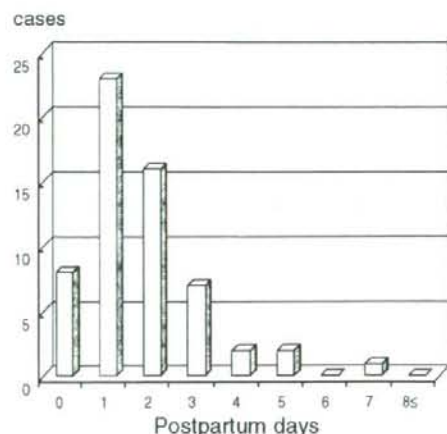


Fig 2. Number of pulmonary thromboembolism cases in obstetrical patients by gestational weeks and postpartum days.