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Venous thromboembolism in the Chinese population — experience in a regional hospital in Hong Kong

華裔人口中的靜脈血栓栓塞——香港一所地區醫院的經驗

Objective. To estimate the incidence and determine the characteristic features of venous thromboembolism in the Hong Kong Chinese population.

Design. Retrospective study.

Setting. Regional hospital, Hong Kong.

Subjects and methods. Data were collected during a period of four years (1997-2000). Patients with duplex doppler ultrasonography or venography-documented venous thromboembolism and new episodes of deep vein thrombosis were identified from Department of Diagnostic Radiology records. Patients with high-probability ventilation-perfusion scans were identified from Department of Nuclear Medicine records and these scans were taken as evidence of pulmonary embolism. Patients with intermediate-probability ventilation-perfusion scans, with pulmonary embolism documented by either pulmonary angiography or spiral computed tomography scan, were also included in the study. Patients with autopsy-verified fatal pulmonary embolism were identified from Department of Pathology records. Patients with deep vein thrombosis at other sites were sought from patient discharge diagnostic coding data. Medical records were reviewed for patient characteristics and conditions associated with the development of venous thromboembolism.

Results. Three hundred and seventy-six Chinese patients had venous thromboembolism during the study period. Of these, 352 had peripheral deep vein thrombosis, five had deep vein thrombosis at other sites (cerebral sinus and portal vein thrombosis), 40 had pulmonary embolism (26 had concomitant deep vein thrombosis), and six had fatal pulmonary embolism shown at autopsy.

Conclusion. The calculated annual incidence of venous thromboembolism in Hong Kong Chinese people was estimated at 16.6 events per 100 000 population, which is lower than incidence rates reported in Caucasians. The four conditions most commonly associated with venous thromboembolism were medical illness, malignancy, orthopaedic surgery, and intravenous drug use. Conditions associated with venous thromboembolism in patients younger than 45 years included intravenous drug use, thrombophilia, pregnancy, and the use of oral contraceptives.

Key words:

Hong Kong;

Incidence;

Thromboembolism;

Venous thrombosis

關鍵詞：

香港；

發生率；

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目的：評估香港華人靜脈血栓栓塞的發生率，並確定其特徵。

設計：回顧研究。

安排：香港一所地區醫院。

患者與方法：此研究從1997到2000年收集數據資料。從放射診斷科的紀錄中，甄別出曾作雙多普勒超聲或靜脈造影靜脈血栓栓塞測試，以及深層靜脈血栓症新發作的患者。從核內科紀錄中甄別出曾作高或然率氣灌掃描患者的紀錄，作為他們患上肺栓塞的證據。本研究也包括由中或然率氣灌掃描，以及由肺部血管造影或螺旋電腦X光斷層攝影掃描診斷的肺部血栓栓塞患者。從病理科紀錄中，甄別經驗屍證明因肺部栓塞而致命的患者。從患者出院紀錄中尋找有其他部位有血管血栓症的患者。本研究也回顧病歷紀錄以總結患者的特徵和引發靜脈血栓栓塞的因素。

結果：研究期間，有376名華人患上靜脈血栓栓塞。其中352人患上週邊深層靜脈血栓症，5人於其他部位有深層靜脈血栓症(腦穴和門靜脈血栓症)，40人患有肺栓塞(26人同時患上縱深血管血栓症)，6人在驗屍時發現患有致命的肺栓塞。

結論：香港華人的靜脈血栓栓塞的年發病率估計為每10萬人16.6，低於現時所知的白人發病率。與靜脈血栓栓塞有關的四個最普遍情況是內科疾病、惡性疾病、矯形外科手術及靜脈注射毒品。年齡少於45歲的患者患上與靜脈血栓栓塞有關的情況包括靜脈注射毒品、血栓形成傾向、懷孕及服用避孕藥。

Introduction

Venous thromboembolism (VTE) is common in Caucasians with an estimated annual incidence of 1.24 to 2.93 per 1000 in the general population.^{1,2} This disease is less common in Asians including Chinese,^{3,4} with little information available about the characteristics of VTE in Chinese people.

Prompt identification of VTE is now possible with the use of non-invasive tools as first-line diagnostic tests, such as the use of duplex doppler ultrasonography (USG)⁵ for deep vein thrombosis (DVT), and ventilation-perfusion (V/Q) scanning for pulmonary embolism (PE). In most hospitals in Hong Kong, the first-line diagnostic test for DVT is USG. Contrast venography (VG) remains a second-line confirmatory tool. A V/Q scan is the first-line screening test for PE. A high-probability V/Q scan according to the Prospective Investigation of Pulmonary Embolism Diagnosis study⁶ is accepted as definitive evidence of PE. If the V/Q scan is of intermediate probability, yet the clinical suspicion of PE is high, either pulmonary angiography (PA) or spiral computed tomography (CT) scanning is used to confirm or exclude the diagnosis of PE.

The aim of this study was to determine the spectrum of VTE disease in a cohort of Chinese patients with diagnosed VTE seen at a regional hospital in Hong Kong during a period of four consecutive years. The incidence of VTE in Chinese would be estimated, and the characteristics of and associated conditions for VTE in Chinese patients explored.

Subjects and methods

Data were collected between 1 January 1997 and 31 December 2000 at the Pamela Youde Nethersole Eastern Hospital, a regional hospital in Hong Kong. Only patients of ethnic Chinese origin were included.

Patients

Deep vein thrombosis

Patients with new episodes of symptomatic DVT documented by USG (ATL HDI3000; Bothell, Washington, US) were identified from Department of Diagnostic Radiology records. A patient with recurrent episodes of DVT during the study period was counted as one patient. Patients with chronic DVT were excluded.

Patients with venous thrombosis at differing sites, including cerebral sinus thrombosis, renal vein thrombosis, and hepatic and portal vein thrombosis were identified from patient discharge diagnostic coding. These thrombotic events were diagnosed by CT scanning, magnetic resonance imaging (MRI), or a combination of these two imaging modalities.

Pulmonary embolism

Patients with high-probability V/Q scans were identified from Department of Nuclear Medicine records. Patients with intermediate-probability V/Q scans but with PE

documented by either spiral CT scanning or PA were also included in the study. Patients who had autopsy-verified fatal PE were identified from Department of Pathology records.

Calculation of incidence of venous thromboembolism

This was based on the size of the population served by the hospital and the percentage of this population estimated to attend the hospital.

Patient characteristics and associated conditions

Medical records of patients were reviewed and associated conditions for VTE were noted. These included medical illness resulting in immobilisation for more than 7 days, malignancies, orthopaedic and other surgical operations, intravenous drug use, acquired/hereditary thrombophilia, haematological disorder, use of oral contraceptives (OC) or hormone replacement therapy, pregnancy, varicose veins, local or major trauma, and previous VTE. Thrombophilia screening had been performed for those patients with recurrent VTE, a strong family history, or VTE at abnormal sites.

Results

Spectrum of venous thromboembolism in the Chinese population

Deep vein thrombosis

During the study period, 352 Chinese patients had new episodes of DVT in their extremities. Of these patients, 349 were diagnosed by USG and three by VG. Sites of DVT included the lower limb in 343 patients (24 had bilateral involvement); the upper limb in six patients; and the neck veins in three patients. Other sites of venous thrombosis included cerebral sinus thrombosis diagnosed by CT scan and MRI in four patients, and portal vein thrombosis demonstrated by CT scan of the abdomen in one patient. These results are summarised in Table 1.

Pulmonary embolism

During the study period, 36 cases of high-probability V/Q scan were identified—22 with concomitant DVT and 14 without DVT. In four patients with intermediate-probability V/Q scan and concomitant peripheral DVT, spiral CT scanning confirmed the presence of PE in three patients and PA in one. Altogether 40 patients had PE—26 had concomitant DVT.

Autopsy findings during the same period revealed six cases of fatal PE. One patient with stroke with

Table 1. Sites of deep vein thrombosis (n=357)

Site of deep vein thrombosis	Patients No. (%)
Lower limb	343 (96.1)
Upper limb	6 (1.7)
Neck veins	3 (0.8)
Cerebral sinus	4 (1.1)
Portal vein	1 (0.3)

Table 2. Spectrum of venous thromboembolism (n=376)

	No. of patients		
	Clinical diagnosis	Autopsy finding	Total
Deep vein thrombosis	326*	-	326
Deep vein thrombosis plus pulmonary embolism	26	4*	30
Pulmonary embolism	14	2	16
Cerebral sinus	4	-	4
Portal vein	1	-	1
Total	371	6	377-1*=376

* One patient with deep vein thrombosis demonstrated by ultrasonography antemortem and fatal pulmonary embolism by autopsy was counted twice

USG-documented DVT antemortem died without clinical symptoms and signs of PE. Three other patients also died without clinical suspicion of PE. Two patients died before treatment for PE could be initiated. Autopsy findings showed the presence of DVT in the lower limbs in four patients and absence in two patients.

The spectrum of VTE in this cohort of 376 Chinese patients is summarised in Table 2.

Incidence of venous thromboembolism in the Chinese population

Pamela Youde Nethersole Eastern Hospital serves a population of 650 000.⁷ Ninety-two percent of Hong Kong residents attend the public health sector⁸ and 94.9% of the local population are ethnic Chinese.⁹ The incidence of symptomatic VTE in Chinese was thus estimated to be 16.6 per 100 000 per year. The calculation is shown below:

$$\frac{\text{Total no. of cases of VTE}}{\text{Total population} \times 0.92 \times \text{no. of years} \times \text{percentage of Chinese}} = \frac{376}{650\,000 \times 0.92 \times 4 \times 0.949}$$

Patient characteristics and associated conditions

Age

The median age was 68 years (range, 21-94 years). The age distribution showed a biphasic pattern—a smaller peak in

the 31 to 40 years age-group for both male and all patients, and a larger peak in the 71 to 80 years age-group for male, female, and all patients. For female patients, the first peak occurred in the 41 to 50 years age-group (n=22), rather than in the 31 to 40 years age-group (n=18) [Fig].

Sex

The total number of female patients with VTE exceeded that of male patients (female:male, 203:173). The difference was further pronounced after excluding cases of intravenous drug use (Table 3).

Associated conditions

Conditions associated with VTE in this group of patients are summarised in Table 4. Medical illnesses resulting in immobilisation for more than 7 days were many and varied, including stroke, congestive heart failure, sepsis, conditions requiring use of a mechanical ventilator, chronic respiratory failure, and severe osteoporosis.

Among the group of patients with malignancies, one patient's DVT antedated the diagnosis of bronchogenic carcinoma. Other patients developed DVT either in the course of treatment or at an advanced stage of the disease. The types of cancer included colonic cancer (n=15), bronchogenic carcinoma (n=10), metastatic cancer of unknown primary (n=9), carcinoma of the cervix (n=5), stomach cancer (n=4), ovarian cancer (n=4), cancer of the

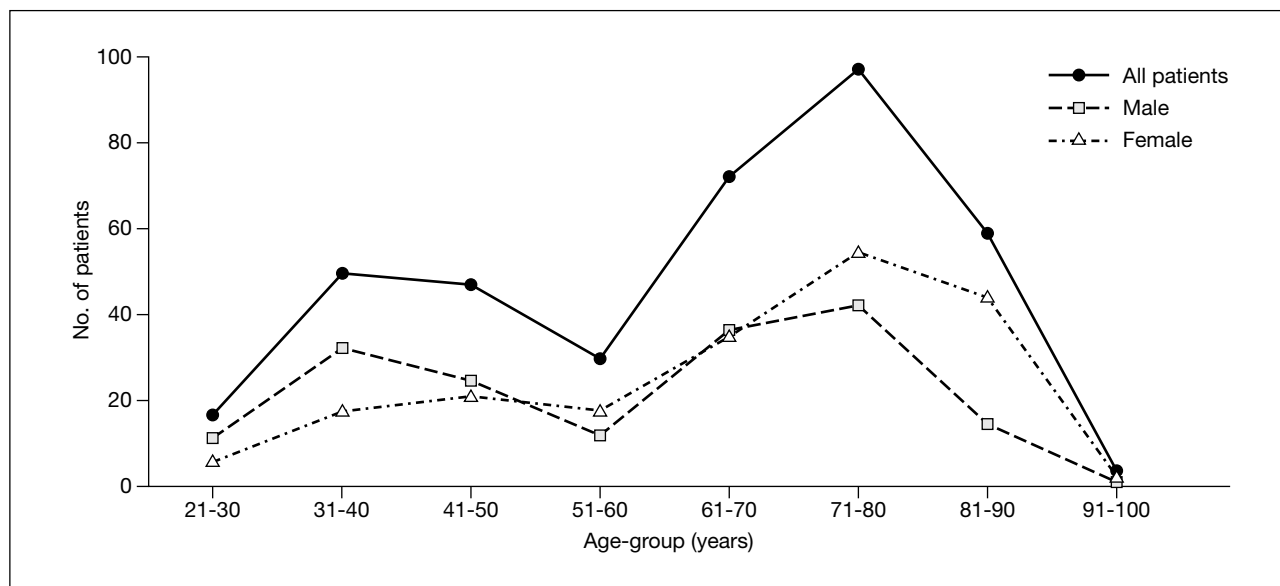


Fig. Age distribution for Chinese patients with venous thromboembolism between 1997 and 2000 (n=376)

Table 3. Comparison of patients with venous thromboembolism by age, sex, and intravenous drug use

Age (years)	No. of patients excluding intravenous drug users		No. of intravenous drug users	
	Male	Female	Male	Female
<50	24	42	44	4
≥50	103	157	2	0
Total	127	199	46	4

Table 4. Risk factors associated with venous thromboembolism in the patient population (n=376)

Risk factors	Median age (range) [years]	Patients No. (%)				Total
		DVT*	PE† ± DVT	CST‡	PVT§	
Medical illness	76 (21-91)	83	16	-	-	99 (26.3)
Malignancy	68.5 (29-89)	56	6	-	-	62 (16.5)
Orthopaedic surgery	75 (31-94)	57	6	-	-	63 (16.8)
Intravenous drug use	37 (24-53)	49	1	-	-	50 (13.3)
Nil	68 (22-87)	29	13	-	-	42 (11.2)
Other surgery	71 (32-82)	15	-	-	-	15 (4.0)
Hereditary thrombophilia (protein S and protein C deficiencies)	35 (22-78)	4	-	2	-	6 (1.6)
Acquired thrombophilia (lupus anticoagulant)	49 (23-69)	3	1	-	-	4 (1.1)
Haematological disease (polycythemia rubra vera)	74	-	-	-	1	1 (0.3)
Oral contraceptive use	40 (34-46)	2	1	4	-	7 (1.9)
Hormonal replacement therapy	50	1	-	-	-	1 (0.3)
Pregnancy	35 (28-39)	5	-	-	-	5 (1.3)
Varicose veins	60 (41-79)	10	1	-	-	11 (2.9)
Local trauma—cannulation of veins	59 (23-69)	4	-	-	-	4 (1.1)
Major trauma	47 (35-56)	2	1	-	-	3 (0.8)
Previous venous thromboembolism	65 (42-86)	3	-	-	-	3 (0.8)

* DVT deep vein thrombosis

† PE pulmonary embolism

‡ CST cerebral sinus thrombosis

§ PVT portal vein thrombosis

^{||} Includes two patients with hereditary thrombophilia who developed cerebral sinus thrombosis

urinary bladder (n=4), breast cancer (n=3), lymphoma (n=3), cholangiocarcinoma (n=2), soft tissue sarcoma (n=2), and nasopharyngeal carcinoma (n=1).

With respect to surgery, postoperative VTE was most frequently associated with orthopaedic surgery, specifically hip replacement (n=36), total knee replacement (n=25), and spinal surgery (n=2). The total number of hip replacements performed during the study period was 174, that of knee replacements was 376, and spinal surgical procedures was 140. Thus, the overall frequency of developing DVT following these three major orthopaedic operations was 9%. The frequency of DVT following hip replacement was 21% and following knee replacement 6.6%. Other surgeries associated with postoperative DVT included neurosurgery (n=7), abdominal surgery (n=5), vascular surgery (n=1), and gynaecological operations (n=2).

Intravenous drug users showed a male preponderance (male:female, 46:4). All showed thrombosed groin veins, except one patient whose axillary vein was thrombosed. Seventeen (34.0%) patients had recurrent VTE.

Thrombophilia screening tests for protein C (PC), protein S (PS), antithrombin deficiencies, activated PC resistance, and lupus anticoagulant (LA) were performed for 16 selected patients in the study. Five patients had PS deficiency, one had PC deficiency, and four had LA. Three of the four patients with LA who developed VTE had additional risk factors such as systemic lupus

erythematosus, and procedural interventions such as knee arthroscopy and endoscopic retrograde cholangiography. One patient with polycythaemia rubra vera developed portal vein thrombosis.

Seven patients developed VTE after taking OC for variable periods ranging from a few days to several years. Of four patients who developed cerebral sinus thrombosis, two also had PS deficiency. One patient with DVT was taking hormone replacement therapy. Pregnancy-associated DVT occurred in five patients—three in the first trimester, one in the postpartum period, and one following termination of pregnancy.

Thrombosis also occurred in association with a number of miscellaneous conditions. Thrombosis was noted following central line placement in four patients. Three patients with adequate renal function after renal transplantation developed extensive DVT in the limbs. Three patients developed DVT after percutaneous coronary angiography. Varicose veins were associated with DVT in 11 patients and one patient developed PE after a vein stripping operation. Major trauma (traffic or other accidents) was associated with VTE in three patients. Three patients had a history of previous DVT as the sole risk factor for the current VTE.

Discussion

The data, collected from a single institution in Hong Kong over four consecutive years, estimated the annual incidence

of VTE in Chinese people to be 16.6 events per 100 000 general population.

The accuracy of this estimate is in part dependent on the sensitivity and specificity of the diagnostic tests used for VTE. In this study, USG was used as the first-line investigative tool, and VG was the second-line diagnostic test for DVT. Ultrasonography has high sensitivity and specificity, especially for the detection of proximal DVT in the lower limbs.¹⁰ Venography is considered the gold standard diagnostic test for DVT but has been largely replaced by USG as the first-line test in the past decade, primarily because VG is an invasive procedure.¹¹ In this study, VG was used to confirm the diagnosis of venous thrombosis in three patients with DVT in the upper limb or neck where USG yielded controversial results. Confirmation of the diagnosis by VG was important for these patients because it affected the choice of therapy. The combination of USG and VG as diagnostic tools should therefore have a high diagnostic yield for peripheral DVT.

The diagnostic test for PE in our series was V/Q scanning. Numerous studies have compared V/Q scanning with PA. The overall positive predictive value of a high-probability V/Q scan has been shown to be 88%.¹² A high-probability V/Q scan is generally considered sufficient evidence to accept the diagnosis of PE. However, PE cannot be considered proven or excluded on the basis of a non-diagnostic V/Q scan. Validation of the V/Q scan result requires either PA, spiral CT, or MRI, especially when the V/Q scan is of intermediate probability and the clinical suspicion of PE is high.¹³ These definitive diagnostic tests were used for only a small proportion of patients in the study. All high-probability V/Q scans in the study were assumed as definitive evidence of PE and, other than four cases with intermediate-probability V/Q scans, the remaining patients did not undergo further investigations and were assumed to have no evidence of PE. This approach allowed potential inclusion of 'false positive' as well as exclusion of 'false negative' cases. This may also explain why the number of patients with DVT and PE was less than that suggested by the literature. According to studies in western populations, approximately 60% of patients with DVT proximal to the calf have asymptomatic PE, and up to 48% of patients with isolated calf vein thrombosis have asymptomatic PE.¹⁴ The annual incidence of DVT in the US is 159 per 100 000, and the overall incidence of PE is 139 per 100 000 per year.¹⁵ In future studies, accurate documentation of PE would require the use of more definitive diagnostic tests. The data in this study also suggest that hospitals should develop protocols for the diagnosis of PE so as to avoid both underdiagnosis and overdiagnosis.

Despite these diagnostic difficulties, this study served to shed light on the condition of VTE in the Chinese population studied. Venous thromboembolism was noted to affect Chinese women more than men, especially when cases of intravenous drug use were excluded. This may reflect the

relative longevity of Chinese females in Hong Kong—the life expectancy at birth for male and female individuals in 1998 was 77.2 and 82.6 years, respectively¹⁶—and the presence of sex-specific risk factors, such as pregnancy and the use of OC. It was, however, difficult to conclude that female sex was a risk factor for VTE because there were no baseline data about the total number of male and female patients admitted during the study period.

Analysis in relation to age revealed that characteristics of patients with VTE differed for elderly patients compared with patients younger than 45 years. The contribution of intravenous drug use to the development of recurrent VTE has received little attention to date and the association is not well documented in the literature. Recently, a report from Glasgow showed that 52.4% of women younger than 40 years presenting with VTE were intravenous drug users.¹⁷ This study suggests that health care providers in Hong Kong should pay more attention to this cause of VTE. As thrombophilia screening tests were performed for only 16 selected patients in this study, it is difficult to comment on the incidence of thrombophilia in Chinese. The limited use of thrombophilia screening tests was partly due to financial constraints and partly in consideration of the low frequency of the condition in Chinese. Previous studies have shown the absence of factor V gene mutation (Arg506→Gln)^{18,19} and the prothrombin gene mutation in Chinese.²⁰ These two genetic mutations have recently been shown to be the most common causes of hereditary thrombophilia in western countries.^{21,22}

The high frequency of DVT after orthopaedic surgery was partly influenced by the common practice of not prescribing prophylactic anticoagulants. It is of interest to note that a high frequency of DVT following hip surgery has been noted previously. A study from Queen Mary Hospital in 1980 showed 53.3% of 45 Chinese patients undergoing hip surgery without prophylaxis developed DVT postoperatively,²³ while a study from Prince of Wales Hospital in 1997 revealed an overall rate of DVT following a hip operation of 37% in 78 Chinese patients. In the latter study, the incidence of DVT did not differ statistically between the group given heparin prophylaxis and the treatment group not given prophylaxis, however.²⁴

This study, in keeping with previous studies, showed a much lower incidence of VTE in Chinese people compared with the reported incidence in the West. Studies from Hong Kong, Taiwan, and Singapore have reported rates of DVT in Chinese patients following general surgery of 2.6%, 7.7%, and 4.7%, respectively.²⁵⁻²⁷ Tso et al²⁸ found the rate of DVT following gynaecological surgery was 2.6% and the frequency of DVT in Chinese stroke patients was 17%.²⁹ Woo et al³⁰ concluded that the annual incidence of PE diagnosed both clinically and by autopsy was 33 per 100 000 hospital admissions. A retrospective autopsy study of PE in Chinese patients in a single university hospital in Hong Kong between 1964 to 1995 revealed a steady increase in the

prevalence of fatal PE—0.21% (1964-74), 1.08% (1975-79), 1.83% (1980-84), 2.77% (1985-90), and 4.7% (1990-94).^{31,32} As both environmental and behavioural factors, in addition to genetic predisposition, contribute to VTE, and Asians including Chinese are moving towards a westernised living style, the incidence of VTE in Chinese is expected to increase with time.

Clinicians in all specialties need to be aware of the condition, especially in patients with risk factors, as VTE is seen across a range of hospital settings. Appropriate hospital guidelines for diagnosis, prophylaxis, and treatment of VTE prepared in consultation with all relevant departments would thus appear useful.

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