

## A 6-year epidemiological study of pulmonary embolism in an emergency department

### 一所急症室為期 6 年之肺栓塞流行病學研究

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**Objective:** To identify the epidemiology and early clinical features of patients with pulmonary embolism with a view to facilitate making the correct diagnosis. **Methodology:** A retrospective study of patients admitted through the emergency department with a discharge diagnosis of pulmonary embolism in the computerised Clinical Management System from 1st January 1999 to 31st December 2004 in a public emergency general hospital in Hong Kong. **Results:** Twenty-two patients were newly diagnosed to have pulmonary embolism and included in the study. The patients' clinical features and investigation findings were analysed. Old age and immobilisation were the most common risk factors identified. Nine patients were found to have deep vein thrombosis but none of them complained of calf pain during consultation in the emergency department. Most patients had symptoms of shortness of breath and chest pain on presentation. Fourteen patients had type 1 respiratory failure. The electrocardiogram and chest X-ray findings were non-specific. All the patients with D-dimer done showed positive results. CT scans were used in all patients to make the final diagnosis. Nineteen patients received low molecular weight heparin followed by warfarin and three patients had thrombolytic therapy. **Conclusion:** Pulmonary embolism is not a commonly diagnosed disease in Hong Kong. The symptoms are non-specific and it is difficult to make the correct diagnosis in the emergency department. (*Hong Kong j.emerg.med.* 2005;12:206-214)

**目的：**識別肺栓塞病者的早期臨床特徵及流行病學以便作出正確的診斷。**方法：**於 1999 年 1 月 1 日至 2004 年 12 月 31 日期間，經香港一所公立普通科醫院的急症室入院，並於出院時臨床管理系統的電腦診斷記錄為肺栓塞的病者，作回顧性的研究。**結果：**這研究包括 22 名新診斷為肺栓塞的病者；並分析病者的臨床特徵及檢驗結果，高齡及不能活動被識別為最常見的風險因素。9 名病者被發現有深層靜脈血栓，但沒有病者於急症室求診時曾申訴小腿疼痛；大部份病者都呈現胸痛及呼吸困難的症狀，其中 14 名病者有第一類型呼吸衰竭。心電圖及胸部放射造影結果並無特異，所有病者的 D-二聚體測試均呈陽性反應，全部病者均使用電腦掃描作確實診斷。19 名病者接受低分子量肝素，隨後使用華法令阻凝血劑治療，其中 3 名病者需接受血栓溶解劑治療。**總結：**肺栓塞在香港並非常見的疾病診斷，其症狀沒有特異性而且很難於急症室作出正確的診斷。

**Keywords:** Anticoagulants, pulmonary embolism, thrombosis, venous thrombosis

**關鍵詞：**抗凝血劑、肺栓塞、血栓、靜脈血栓

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## Introduction

Pulmonary embolism (PE), first recognised by Rudolf Virchow in the 19th century, is all along a main threat to human life. The incidence of pulmonary embolism has been estimated at 2.5% to 5%, causing 50,000 to

100,000 deaths in the United States annually.<sup>1</sup> Although pulmonary embolism is well known to be relatively rare in Chinese, its incidence seems to be on the rising trend. Chan and Hoaglund reported a prevalence of pulmonary embolism of 0.75% in the adult Hong Kong Chinese population in 1980.<sup>2</sup> A recent study in the 90's showed the prevalence rose to 4.7%.<sup>2</sup> The mortality rate is also very high. It is 30-50% in untreated patients and 15% in the first three months even if treated. The mortality rate is decreasing since 1989, reflecting improvements in diagnosis and treatment. In the International Cooperative Pulmonary Embolism Registry of 2,454 patients from seven countries, the 3-month mortality rate was 17.4%.<sup>3-7</sup> The non-specific presenting signs and symptoms and the lack of a single, non-invasive, easily accessible and accurate test make diagnosis difficult, especially in Chinese localities where the prevalence rate of pulmonary embolism is relatively low.

## Study setting and methods

This study was carried out at North District Hospital. It is a general public hospital serving a population of around 300,000 in the northeastern part of the New Territories of Hong Kong. This was a retrospective study basing on a computer list generated from the Health Information and Records Department of the hospital. Cases admitted through the Emergency Department with the principle discharge diagnosis of pulmonary embolism in the period from 1st January 1999 to 31st December 2004 were included. All patients with no previous history of pulmonary embolism or deep vein thrombosis (DVT) were included. Patients with past history of pulmonary

embolism were excluded because this could bias the subsequent history taking and clinical findings. Patients admitted for other reasons like surgical or orthopaedic problems and developed pulmonary embolisms during hospitalisation were also excluded. The risk factors, clinical presentations, investigation results and treatment methods were analysed.

## Results and background statistics

During the five-year study period, there was a total emergency attendance of 606,155 with total admission of 106,774 (admission rate 17.6%). Twenty-two patients were newly diagnosed to have pulmonary embolism on discharge. There were 13 female and 9 male, with age ranging from 39 to 84 years (mean 64).

Among the 22 patients, 9 of them were above 70 years old. Five patients were bed or chair bound before the incidence. However, nearly a quarter of our patients had no obvious risk factors identified (Table 1).

The major complaints and parameters that were written down on the emergency records by the triage nurses and the attending medical officers were reviewed and analysed (Table 2). The most common presenting symptoms were shortness of breath, tachycardia (pulse rate >100/min) and chest pain. Only one patient (4.5%) presented with no chest pain or shortness of breath. Nine patients (40.9%) turned out to have DVT but none of them complained of leg pain and no DVT had been diagnosed before admission.

**Table 1.** Risk factors in the 22 patients

Risk factor	Number (percentage)
Age >70	9 (40.9%)
Immobilisation	5 (22.7%)
Smoker	4 (18.2%)
Malignancy	2 (9.1%)
Hormonal injection	1 (4.5%)
Nephrotic syndrome	1 (4.5%)
No obvious risk factor	5 (22.7%)

**Table 2.** Clinical features in the 22 patients

Clinical feature	Number of patients
Shortness of breath	19 (86.4%)
Tachycardia (>100/min)	17 (77.3%)
Chest pain	13 (59.1%)
Dizziness	6 (27.3%)
O <sub>2</sub> saturation <95%	5 (22.7%)
Syncope	3 (13.6%)
Shock	1 (4.5%)
Cough only	1 (4.5%)
Haemoptysis	1 (4.5%)

The Wells' clinical scores of the 22 patients were calculated. Only 7 patients (31.8%) fell into the high-risk group, 4 patients (18.2%) fell into the medium risk group and half of them fell into the low risk group.

Electrocardiogram (ECG) findings were non-specific. Seventeen patients (77.3%) had sinus tachycardia, 8 (36.4%) had the typical  $S_1Q_3T_3$  ECG changes, 8 (36.4%) had right ventricular strain pattern, one had simple atrial fibrillation, while 5 patients (22.7%) had normal ECG.

Most of the patients had normal chest X-ray (CXR) findings. Only 2 (9.1%) had mild oligoemic changes and one (4.5%) had infiltrates.

All patients had arterial blood gas (ABG) done. Fourteen patients (63.6%) presented with type 1 respiratory failure, 7 patients (31.8%) had normal  $PaO_2$  and decreased  $PaCO_2$ , and one had normal result.

Fourteen patients had D-dimer latex agglutination test performed and all of them had a positive result.

Nine out of the 22 patients (40.9%) were found to have DVT in the proximal veins by ultrasound.

All patients had CT scan done. Seven patients (31.8%) showed large emboli in the main branches while the rest had only small peripheral emboli.

Nineteen patients received low molecular weight heparin followed by warfarin. Three patients had thrombolytic treatment due to persistent shock or hypoxia despite supportive treatment. Three patients died during hospitalisation (mortality rate 13.6%). Three patients were planned to have life long warfarinisation, two were due to the presence of malignancy and one was due to young age idiopathic PE. All other patients had or planned to have warfarin for six months.

## Discussion

### *Pathophysiology and risk factors*

Deep vein thrombosis is present in 50-70% of patients

with pulmonary embolism and 50% of patients with proximal DVT of legs would have pulmonary embolism.<sup>5,8</sup> However, only 40.9% of our patients were found to have DVT. Most of the clots are initially found in the iliac, deep femoral or popliteal veins. They can also come from the pelvic, renal, and upper extremity veins, right heart chambers and central venous catheter sites. The emboli travel to the lungs, causing pulmonary vascular obstruction, increase in vascular resistance and resulting in right heart dysfunction. The formation of thrombus is multifactorial and the risk factors have been well identified.<sup>1,3,9</sup>

The PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study showed that patients with pulmonary embolism were more likely to have one or more risk factors than other patients. Studies showed that more than 80-90% of the patients with pulmonary embolism had at least one major risk factor. The risk factors fit into Virchow's triad of venous stasis, venous wall injury and increased coagulability of blood. They can be classified into primary and secondary factors (Table 3).<sup>1,8,10,11</sup>

### *Clinical presentations*

The clinical features of pulmonary embolism are very non-specific. The classic triads of clinical features are dyspnoea, chest pain and haemoptysis.<sup>12</sup> It can be classified into three categories. Acute minor pulmonary embolism, with sudden obstruction of less than 50% of the pulmonary circulation, presents with shortness of breath on exertion, pleuritic pain, haemoptysis, and shallow rapid breathing. Acute massive pulmonary embolism, with sudden obstruction of more than 50% of the pulmonary circulation, presents with right heart failure, drop in blood pressure and hypoxaemia. Subacute massive pulmonary embolism, caused by multiple small sized emboli, gives the right heart time to adapt and presents with shortness of breath, decreased exercise tolerance, increased venous pressure but normal blood pressure and pulse.<sup>13,14</sup>

Series of studies showed that 97% of patients with pulmonary embolism without other cardiac or lung problem presented with chest pain, sudden onset dyspnoea (>20 breaths/min) or tachycardia. In the groups of patients with heart or lung problem, 97%

**Table 3.** Risk factors

<b>(A) Primary or hereditary</b>	
Deficiency of Protein C or S or Antithrombin III	Excessive plasminogen activator inhibitor
Resistance to activated Protein C	Congenital dysfibrinogenaemia
Mutation of Prothrombin 20210A	Factor XII deficiency
Hyperhomocysteinaemia	Dysplasminogenaemia
Plasminogen deficiency	Factor V Leiden mutation
<b>(B) Secondary or acquired</b>	
Trauma / fractures	Surgery
Stroke	Prolonged immobilisation
Old age	Obesity
Smoking	Long travel
Pregnancy / puerperium	Oral contraception
Crohn's disease	Heart failure
Active malignancy	Nephrotic syndrome
Central venous catheter insertion	Hyperviscosity
Platelet abnormalities	Vasculitis

would present with increased shortness of breath, chest pain or syncope.<sup>1,8,13,14</sup>

Chest pain, due to distal emboli causing pleural irritation, is one of the commonest presentations. Shortness of breath means more central pulmonary embolism. However, clots obstructing less than 50% of the pulmonary vessels can be asymptomatic. It can be followed by anginal chest pain due to right heart ischaemia. Syncope, shock or even sudden cardiac arrest will be the presenting symptom if there are large central emboli. Other findings include low-grade fever, pleural rubs, rales and cyanosis.<sup>1,12</sup>

Although the presence of certain clinical features cannot be used to make a diagnosis, the absence of some clinical features makes pulmonary embolism unlikely. Only 10% of the patients would have no dyspnoea and tachypnoea together and only 3% have neither of these nor chest pain. The absence of chest pain, dyspnoea and tachypnoea can exclude the diagnosis of PE.<sup>13</sup> The differential diagnoses include chronic obstructive pulmonary disease, asthma, pneumonia, pneumothorax, pericarditis and myocarditis.<sup>1</sup>

### ***Clinical scoring system***

There are various scoring systems. One popular scoring system is the Wells' scoring system (Table 4). Wells and colleagues used an assessment of symptoms and signs, the presence of an alternative diagnosis and risk factors to categorise a patient into low, intermediate or high probability of PE. Various clinical features are used to calculate the final score. The scoring system has a maximum of 12.5 points. A total score <2 points makes pulmonary embolism unlikely while >6 points makes the probability high. The prevalence rates are 2%, 19% & 50% respectively.<sup>14</sup> Half of our patients fell into the low risk group, so we should not rely solely on the score to make the diagnosis of PE.

### ***Electrocardiogram***

ECG changes are very non-specific and should not be used to rule in or rule out the diagnosis. The main value of it is to exclude other possible causes e.g. acute myocardial infarction, pericarditis and acute coronary syndrome. Various studies showed that 15-27% of ECG were normal, compared with 22.7% of our patients having normal ECG. The most common findings are non-specific ST segment-T wave changes with sinus tachycardia. In minor pulmonary embolism,

**Table 4.** Wells' clinical scoring system for pulmonary embolism

<u>Clinical feature</u>	<u>Score</u>
Signs and symptoms of deep vein thrombosis	3
Heart rate >100/min	1.5
Immobilisation or surgery in the previous 4 weeks	1.5
Previous deep vein thrombosis / pulmonary embolism	1.5
Haemoptysis	1
Malignancy (on treatment, treated in last 6 months or palliative)	1
An alternative diagnosis is less likely	3
<b>Clinical probability</b>	Low = 0 - 1 Moderate = 2 - 6 High $\geq$ 7

the ECG may show sinus tachycardia only. In massive pulmonary embolism, right heart strain (right axis deviation, new right bundle branch block, anterior and inferior T inversion, P pulmonale) may be found. The classic  $S_1Q_3T_3$  (Figure 1), only found in 15-25% of patients with pulmonary embolism, has sensitivity and specificity of 54% and 62% respectively.<sup>13-16</sup>

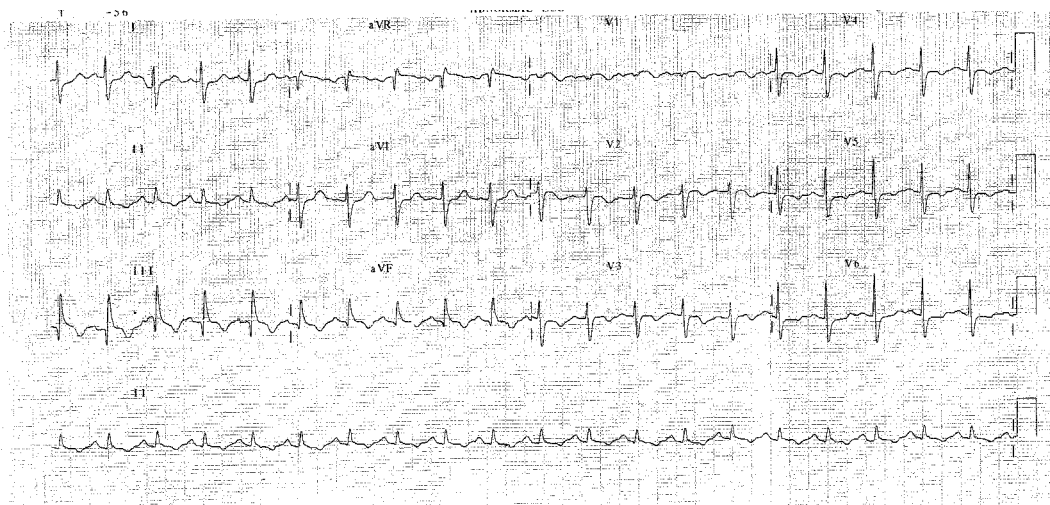
### ***Chest X-ray***

CXR findings are also non-specific but can exclude other problems like pneumothorax, pneumonia and pleural effusion.<sup>9</sup> Even in massive pulmonary embolism, the CXR can be normal. A study of 2,454

patients with PE found cardiac enlargement in 27%, normal CXR in 24%, pleural effusion in 23%, pulmonary artery enlargement in 19%, atelectasis in 18%, pulmonary infiltrates in 17%, and elevated hemidiaphragm in 2%.<sup>17</sup> The classic signs are Westermark's sign (oligaemia) and Hampton's hump (wedge-shaped pulmonary opacity).<sup>1,10</sup> In a patient presenting with severe dyspnoea but normal CXR, the diagnosis of pulmonary embolism should be considered.<sup>18</sup>

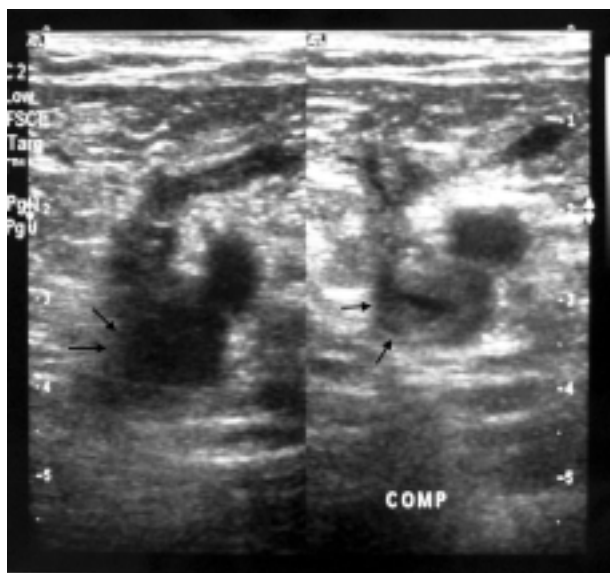
### ***Doppler ultrasound for deep vein thrombosis***

Evidence of DVT has been found in 50-70% of



**Figure 1.** Electrocardiogram of a patient with pulmonary embolism, showing  $S_1Q_3T_3$ , T inversion in  $V_2$  to  $V_3$ , tachycardia and right axis deviation.

patients with pulmonary embolism. It is believed that the rest with no DVT found actually had DVT but the whole thrombus had already detached and embolised. It is believed that 50% of patients with proximal DVT would have pulmonary embolism. Other sources of emboli including iliac veins, renal veins, axillary veins, and right heart, are very rare. However, detection of proximal DVT is an indication to start anticoagulant treatment regardless of the presence of clinical evidence of pulmonary embolism (Figures 2 & 3). As ultrasound for the detection of proximal DVT is non-invasive with a high degree of



**Figure 2.** Doppler Ultrasound showing thrombus in femoral vein which is not compressible (arrows).



**Figure 3.** Thrombus in common femoral vein (T).

accuracy, readily available in most emergency departments and can be performed repeatedly, it should be done in all patients suspected to have pulmonary embolism. Doppler imaging, if available, can even detect small thrombosis of the distal veins.<sup>12,19</sup>

### ***Echocardiogram***

Echocardiogram can be performed at the bedside safely, easily and repeatedly. Although it cannot detect pulmonary embolism directly, it can be used to reveal a floating thrombus trapped in the right atrium or ventricle, hypokinetic right ventricle, dilated and non-collapsible inferior vena cava or severe tricuspid regurgitation. It is also helpful in excluding other causes like cardiac tamponade, endocarditis and aortic dissection.<sup>14,20</sup>

### ***Blood gas***

Arterial blood gas has insufficient specificity and sensitivity to rule in or rule out PE. The characteristic changes are decreased PaO<sub>2</sub> and normal or decreased PaCO<sub>2</sub> due to hyperventilation.<sup>1</sup> A study by Cvitanic found that 76% of patients with PE would have hypoxemia and 93% would have either hypoxemia or hypocapnia. Increased alveolar-arterial O<sub>2</sub> gradient was found in 98% of patients with PE.<sup>1</sup>

### ***Biomarkers***

D-dimers are degradation products formed when cross-linked fibrin contained within a thrombus is proteolyzed by plasmin. There are various types of D-dimer screening tests, including the classic ELISA (enzyme-linked immunosorbent assay), rapid ELISA, latex agglutination assay and bedside SimpliRED test. ELISA has more than 99% sensitivity in acute pulmonary embolism while latex agglutination assay has low sensitivity of 50% to 60% only.<sup>1,9,12</sup> It may be positive not only in pulmonary embolism but also in disseminated intravascular coagulation, malignancy, post-trauma, post-operation, severe infection, heart failure and renal failure.<sup>1</sup> D-dimers are not useful in confirming the diagnosis but the test is useful in ruling out pulmonary embolism. In combination with a non-high clinical probability for pulmonary embolism, with normal findings on other non-invasive tests, negative D-dimer levels mean that anticoagulation therapy can

be withheld safely without further investigation.<sup>3</sup> However, it should not be used as the only test to determine the management. False negative results can occur if the test is done too early or too late and also if the thrombus is small. This is more common in the old age group as D-dimer levels are lower in this group of patients.<sup>19</sup>

Another new cardiac biomarker that is under hot discussion recently is the troponins, which are the most sensitive and specific markers of myocardial cell damage. Raised concentrations of troponins are associated with higher in-hospital mortality in patients with pulmonary embolism, so it may serve as a guide to the aggressiveness of the therapy, especially in the use of thrombolytics.<sup>3</sup>

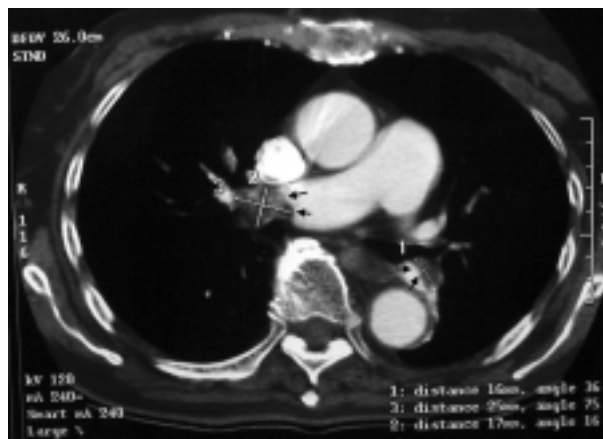
### ***Computed tomographic pulmonary angiography (CTPA)***

Recent technological advances in CT make CTPA a major diagnostic tool in PE. All of our patients had CT done to confirm the diagnosis. The British Thoracic Society recommends CTPA as the initial lung imaging for non-massive pulmonary embolism.<sup>21</sup> Unlike pulmonary angiography, it is non-invasive, more easily accessible and allowing direct visualisation of the emboli. Acute pulmonary emboli present as hypo-attenuating filling defects within the vessels, surrounded by opacified blood (Figure 4). Other signs include pleural-based densities (Figure 5), atelectasis, dilatation of pulmonary arteries and pleural effusion.<sup>22</sup> It can also provide significant information for other possible abnormalities in the lung.<sup>12,14</sup> Multiple studies revealed that it had high sensitivity and specificity.<sup>23</sup> The reported sensitivity of the new helical CT scanning varies from 57% to 100% with specificity ranging from 78% to 100%. It has high sensitivity in detecting thrombi in the main (100%) or lobar pulmonary arteries (85%) but a negative result cannot rule out small subsegmental pulmonary artery thrombus since the sensitivity for the latter is only 5-30%.<sup>22</sup> However, series of studies found that even if small peripheral emboli were missed, morbidity or prognosis was not altered.<sup>22,23</sup> The rate of developing pulmonary emboli after a negative CTPA is similar to that after a negative pulmonary angiogram.<sup>24</sup> Recent studies and meta-

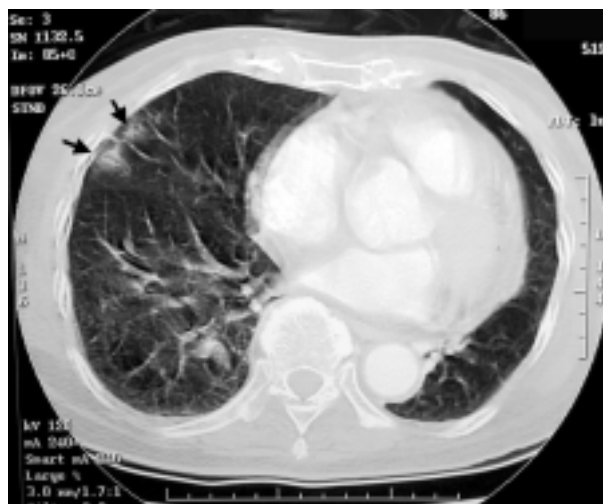
analysis have concluded that if there is a normal good quality CTPA, further investigation for pulmonary embolism is not necessary.<sup>21</sup> CT venography can also be done together with CTPA to evaluate DVT.

### ***Pulmonary angiography and ventilation-perfusion lung scan***

None of our patients underwent pulmonary angiography or ventilation-perfusion lung scan (V/Q scan). Pulmonary angiography is still considered to be the gold standard in the diagnosis of pulmonary embolism; however it is invasive, costly and not available in all hospitals.<sup>18,19,25</sup> It is also associated with a 3.5-6% complication rate and a mortality rate of 0.2-0.5%.<sup>15</sup>



**Figure 4.** CT pulmonary angiogram showing emboli in the left and right pulmonary arteries (arrows).



**Figure 5.** CT pulmonary angiogram demonstrating peripheral pulmonary infarction in a patient with pulmonary embolism (arrows).

### ***Treatment***

The objective is to prevent death and recurrence. General supportive measures including intravenous fluid, high flow oxygen, analgesic and close monitoring of vital signs should be given immediately.

Anticoagulation remains the mainstay of treatment of PE, acting to prevent clot propagation and allowing endogenous fibrinolytic activity to dissolve existing thromboemboli. The common anticoagulants are unfractionated heparin (UFH), low molecular weight heparin (LMWH), and warfarin. With systemic heparinization, the mortality can be reduced from 18.4% to 2.5%.<sup>1</sup>

UFH binds to antithrombin (AT) and accelerates its rate of coagulation enzyme inhibition.<sup>26,27</sup> The traditional approach of heparin is to give a bolus dose of 5,000-10,000 units followed by continuous infusion, starting at 30,000-40,000 units per 24 hours, to maintain a partial thromboplastin time (APTT) in the range of 1.5-2.5 times the control value.<sup>27-29</sup> The risk of major bleeding is 2%.<sup>27</sup>

Low molecular weight heparin, produced by controlled enzymatic or chemical depolymerization of UFH, has less non-specific binding to endothelium, macrophages and plasma protein other than AT. It has the advantage of more predictable anticoagulant response and can be given subcutaneously once daily. It is not necessary to be monitored closely. The dosing regimens for the various preparations are different.<sup>27,28</sup> It was found to be as effective and safe as UFH but with a lower mortality.<sup>27,29</sup> A recent meta-analysis by Quinlan et al analysed 14 trials involving 2,110 patients and found that LMWH had a statistically non-significant decrease in recurrent pulmonary embolism and bleeding complications.<sup>30</sup>

Warfarin, an oral vitamin K antagonist, should be started at a dose of 5 mg after the initiation of heparin, which is continued for at least five days, until a stable dose of warfarin is achieved. The aim is to keep the INR (international normalised ratio) within 2.0-3.0.<sup>29,31</sup> When a major reversible risk factor can be identified and removed, the risk of recurrence is 3% only in the first

year and 10% in the first five years. Warfarin should be continued for six months. Life long warfarin should be considered in patients with a high risk of recurrence, e.g. patients with malignancy or idiopathic pulmonary embolism, since the recurrence rate is 10% in the first year and 30% within five years if left untreated.<sup>27,32</sup> Thrombolytic agents dissolve thrombi by activating plasminogen to plasmin which degrades fibrin. The use of thrombolytic therapy has the advantages of faster improvement in pulmonary perfusion because of rapid clot lysis, lower incidence of relapse and lower risk of pulmonary hypertension.<sup>26,33</sup> Common thrombolytic agents include streptokinase, urokinase, rt-PA, and reteplase. A meta-analysis by Wan et al, including 11 trials with 748 patients, found that there was no evidence that thrombolytic therapy was better than heparin in non-selected cases.<sup>6</sup> Thrombolytic therapy then should be used in massive PE with clinical shock, in patients with recurrent PE despite anticoagulation or one with contraindication to systemic anticoagulants.<sup>6,21,26</sup>

Other means include embolectomy, either by transvenous catheter or by open surgery, vena cava filters and catheter-directed thrombolysis.<sup>21,33,34</sup>

### **Conclusion**

It is not easy to make the correct diagnosis of pulmonary embolism in emergency departments serving mainly a Chinese population as the prevalent rate is not high, but it can be fatal if the diagnosis is missed. Pulmonary embolism must be put high on the list of differential diagnoses if the presenting symptoms are dyspnoea, chest pain, tachycardia, tachypnoea and/or dizziness. Clinical scoring systems may not be very accurate but by combining with other simple investigations like ECG, CXR, ABG, lower extremity venous ultrasound, D-dimer test, hopefully we can go to the right track. Helical CTPA scan can confirm most of the cases with major emboli and is becoming the first line investigation if pulmonary embolism is suspected. The first line treatment should be LMWH followed by warfarin and treatment should be started as soon as the diagnosis is confirmed or even when suspicion is high in order to reduce the mortality and complications.

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