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Diagnostic and therapeutic approach to acute pulmonary embolism in an emergency department

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Abstract. – **Pulmonary embolism (PE) is the obstruction of the pulmonary arteries by the dislodging and embolization of thrombotic material coming in most cases from the deep veins of the leg. PE is a relatively common disease with an estimated annual incidence up to 37 cases diagnosed per 100,000 persons it is the third cause of death in the United States. Clinical signs and symptoms are non specific and in the 70% of cases there isn't a correct diagnosis. The aim of this review is to summarize the state of the art of the diagnostic and treatment algorithms of PE in the evidence based medicine in order to minimize the "clinician gestalt" by the only guide for the early diagnosis and treatment of the disease. A correct diagnosis based on pre test probability, the use of computed tomographic pulmonary angiography, early anticoagulation/fibrinolysis started in the Emergency Department can change the natural history of the disease. In perspective, a combined approach of localyzed fibrinolysis and mechanical fragmentation could improve the overall outcome of these patients.**

Key Words:

Pulmonary embolism, Emergency, Diagnosis, Therapy, Heparin, Fibrinolysis.

Introduction and Definition

Definition

Pulmonary embolism (PE) is the obstruction of the pulmonary arteries by the dislodging and embolization of thrombotic material coming in most cases from the deep veins of the leg, pelvis and arms. PE ranges from partial clinical unimportant thromboembolism of the small circle to large massive obstruction of the pulmonary arteries with sudden onset of breathlessness, right ventricular critical hypokinesis and death (Figure 1). Actually this term includes also embolism from many other sources such as amniotic fluid, gasses, sepsis, tumors and bone marrow[1].

Pulmonary embolism (PE) and deep vein thrombosis (DVT) should be considered part of the same pathological process.

Epidemiology

PE is a relatively common disease with an estimated annual incidence in the United States up to 37 cases diagnosed per 100,000 persons and it is the third cause of death. Autoptical data and clinical reports show an incidence of 100-200 cases for 100,000 persons per year[2,3] with 70% of cases undiagnosed because of the wide spectrum of clinical signs and symptoms of PE that are not specific.

A correlation between autoptical and clinical findings shows that on 100 cases of PE 30% were correctly diagnosed soon after the presentation of symptoms. This group had a three months mortality rate of 5.2% (17.5% of this particular group)[4]. Seventy percent were not diagnosed; in this group 10% dies within the first hour (14.28%), 20% dies without a correct diagnosis (28.58%), 40% was alive without a correct diagnosis (57.14%).

There is a great variation of data in the epidemiology of PE in different countries not clearly depending by the accuracy of diagnosis or local factors. In any case untreated PE has a high mortality, althought an early diagnosis and an appropriate treatment significantly reduce the risk of death (42,86% in the undiagnosed group versus 17.5% of the diagnosed one). Even if we do not mind the undi-

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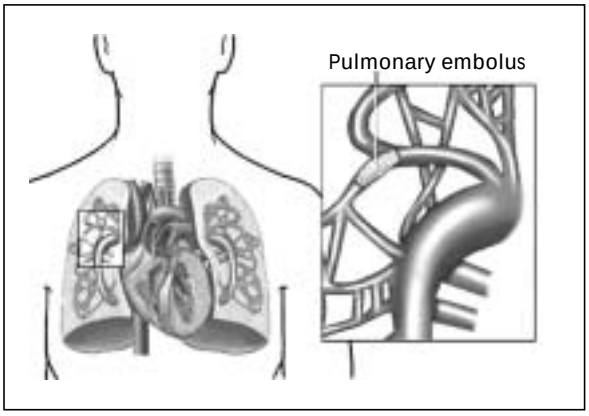

Figure 1. Pulmonary embolus.

Table I. Major predisposing factors for PE.

Surgery	Major abdominal/pelvic surgery Hip/knee replacement Postoperative intensive care
Obstetric late pregnancy	Cesarian section puerperium
Malignancy	Abdominal/pelvic Advanced/metastatic
Reduced mobility	Hospitalization Institutional care
Lower limb fractures	
Previous proven VTE	

The major predisposing risk factors for PE (relative risk 5-20).

agnosed deaths within the first hour, that we should assume not to be avoided also in presence of a correct diagnosis and therapy, the early diagnosis and therapy seem to significantly change the natural history of the disease (28.58% of deaths in the undiagnosed group versus 17.5% of the diagnosed one) (Figure 2).

Pathophysiology

Pulmonary embolism isn't an isolated disease but in most cases is a complication of deep vein thrombosis (DVT) and a consequence of venous thromboembolism (VTE) so that predisposing factors for DVT and VTE are the same of PE.

All known risks factors for DVT, VTE and PE can be included in the Virchow's Triad:

- Venostasis
- Hypercoagulability
- Vascular wall inflammation.

The major predisposing factors (relative risk 5-20) for VTE are summarized in Table I. The minor predisposing factors (relative risk 2-4) are summarized in Table II.

Trombi after developing in deep veins may embolize to the pulmonary arteries. The ileofemoral system is the commonest site of significant PE, but smaller veins (eg. axillary) may still produce clinically and haemodynamically significant PE. Of course proximal clots are larger, fragile and are prone to dislodge and travel up to the pulmonary circulation causing PE. Pulmonary arterial obstruction and the release by platelets of vasoactive agents, such serotonin, elevate pulmonary vascular resistance. The resulting increase in alveolar dead space and the redistribution of the blood flow

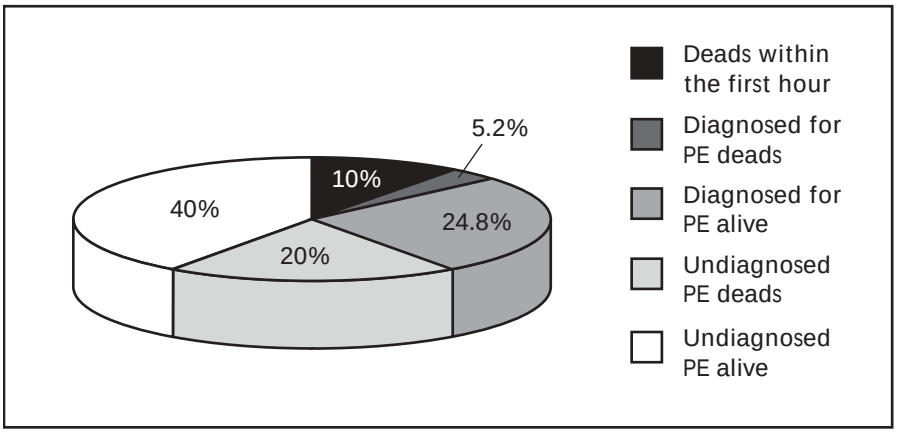

Figure 2. Mortality of patients with PE

Table II. Minor predisposing factors for PE.

Cardiovascular	Congenital hearts disease
	Congestive cardiac failure
	hypertension
	Superficial vein thrombosis
	Indwelling vein catheter
Oestrogen	Oral contraceptive
	Hormone replacement therapy
Miscellaneous	COPD
	Neurological disability
	Occult malignancy
	Thrombotic disorders
	Lupus anticoagulant
	High homocystine level
	Factor V Leiden
	Lack of protein C, S, AT III
	Long distance/sedentary travel
	Obesity
	Smoke of cigarettes

The minor predisposing risk factors for PE (relative risk 2-4).

(which creates areas of decreased ventilation to perfusion) impair the gas exchange; moreover, the stimulation of irritant receptors causes alveolar hyperventilation. The reflex bronchocostriction increased airway resistance and lung edema decrease the pulmonary compliance[5]. As right ventricular afterloads increases, tension rises in the right ventricular wall and may lead to dilation, dysfunction, and ischemia of the right ventricle.

Diagnosis

The diagnosis of PE is a challenging task because of the wide spectrum of non specific symptoms and signs so that most patients with suggestive symptoms do not have the disease. Clinical features vary depending on the size of embolus (thus the degree of pulmonary vascular bed obstruction) and the ability of the right ventricle to respond to increased afterload and range from none asymptomatic to circulatory collapse and death.

Common Symptoms/Signs:

- Breathlessness/dyspnoea is the most frequent symptom and tachypnoea is its most frequent sign
- Anxiety
- Tachycardia (hr > 100 bpm)

Uncommon Symptoms/Signs:

- Cough
- Pleuritic chest pain
- Haemoptysis
- Fainting/syncope
- Fever
- Signs of right ventricular function compromise (jugular distension – S3 or S4)
- Accentuated pulmonary component of the second heart sound (S2)
- Swelling
- Sings of venous thrombosis of inferior limbs and edema
- Cianosys.

PE should be considered whenever a patients presents with any of the above symptom complexes particularly in presence of known risk factors or when there is no clear alternative.

Because of the wide spectrum of clinical signs and symptoms of PE that are not specific and in order to avoid the less experienced "clinician's gestalt" be the only guide for the diagnosis of PE, in the last ten years the pre test probability scores where defined in the international literature.

Pre test probability try to find a simple clinical model to categorize patients with a probability of PE. We usually refer to "the simplified Wells scoring system" and to the "Clinical prediction rule of Geneva" (Table III).

Table III. The simplified Wells scoring system.

	Score
Clinical signs/symptoms of deep venous thrombosis (minimum of leg swelling and pain with palpation of the deep veins of the leg)	3
No alternative diagnosis likely or more likely than pulmonary embolism	3
Heart rate > 100 bpm	1.5
Immobilization or surgery in the last 4 weeks	1.5
Previous history of deep venous thrombosis or pulmonary embolism	1.5
Hemophtysis/cancer treated within last 6 months	1.0
Category scores are as follows low < 2 post test probability 1.3%:	
Moderate 2-6	16.2%
High > 6	0.6%

[Wells et al. 2001][5].

Table IV. The clinical prediction rule by Wiki et al.

	Point Score
Age 60-79	1
Age > 80	2
Previous pulmonary emboli or deep venous thrombosis	2
Recent Surgery	3
Pulse rate > 100/min	1
$PaCO_2$, KPa < 4.8	2
$PaCO_2$, KPa 4.8-5.19	1
PaO_2, KPa < 6.5	4
PaO_2, KPa 6.5-7.99	3
PaO_2, KPa 8-9.49	2
PaO_2, Kpa 9.5-10.99	1
Chest radiography with platelik e atelectasis	1
Chest radiography with elevated hemidiaphragm	1
Categories scores as follows < 5 low pre test probability	*10% of PE post test probability*
5-8 intermediate pre-test probability	38% of PE post test probability
9-16 high pre-test probability	81% of PE post test probability

[Wells et al. 2001][5].

Wiki et al[6] pooled clinical data and physical examination together with results of the chest radiography, electrocardiogram and arterial blood gas analysis collected during three studies, involving 986 consecutive patients. A seven variable rules were derived by logistic regression and statistically validated. A score was used to estimate the pre-test probability of PE (Table IV).

At the moment is possible to increase the pretests utility assessing D-Dimer levels.

D-Dimer Test

D-Dimer test has been generally accepted as cheap, non invasive and highly sensitive for the exclusion of PE, but it is still not part of diagnostic algorithm in many centers[7].

In the presence of thrombin, fibrinogen is cleaved to form fibrin monomers, which are subsequentely stabilized by thrombin activated factor XIII. Covalent cross linkages in the D-domain region of fibrin produce an insoluble fibrin clot. The presence of the fibrin clot, in turn, triggers plasmin to lyse the clot as well as fibrinogen. Lysis of the fibrin clot generates cross linked fibrin degradation products containing D-Dimers (Figure 3).

Most patient with PE have some endogenous (although clinical ineffective) fibrinolysis. When plasmin digests cross linked fibrin from the pulmonary embolus that has formed, D-Dimers are released in the plasma and can be recognized by commercially available monoclonal antibodies. The plasma D-

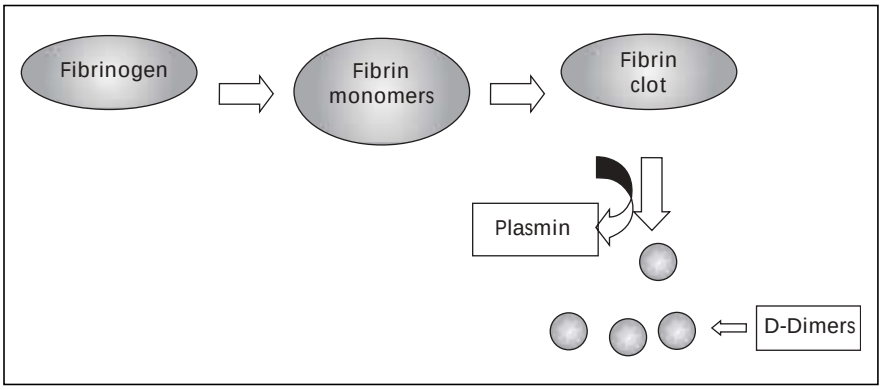

Figure 3. D-Dimer genesis.

Dimer ELISA is highly sensitive but non specific for the diagnosis of PE, with a high negative predictive value. Generally, a finding of more than 500 ng of D-Dimer per milliliter is considered abnormal, and such levels are present in more than 90% of patients. Conversely, the finding of a normal D-Dimer level escludes the presence of PE in more than 90% of cases.

In summary, blood D-Dimer assay should only be considered following assessment of pre test clinical probability in patients with low clinical probability. In fact, the significance of a negative D dimer test (D-Dimer < 500 ng/ml) is to reliably esclude PE in patients with low (simpli RED, Vidas, MDA) or intermediate (Vidas, MDA) pre-test clinical probability; such patients do not require imaging for VTE or PE[8].

Blood Gas Analysis

The most common arterial blood gas analysis abnormality is respiratory alkalosis with hypocapnia and hypoxemia. Respiratory alkalosis and hypocapnia result from hyperventilation. Hypoxemia is the result of increased dead space from the clot occluding pulmonary vessels and causing underperfused but well ventilated alveoli. However the value of these tests can range from normal to typical and are non specific for diagnosis.

Electrocardiography

Electrocardiography is non specific and may shows the signs of right sided heart failure (Figure 4).

The most common electrocardiographic findings associated to PE are:

- right bundle-branch block – right axis deviation
- S wave in I and aVL > 1.5 mm (or r:s ratio < 1)
- Q in leads III and aVF
- T wave inversion in lead 3, aVF and/or leads V1-4
- prominent P wave II, III and aVF
- S1, Q3, T3 pattern o S1, S2, S3 pattern
- ST ischaemic, T wave aspecific alterations in anteroseptal and right leads
- Synusal tachicardia, flutter, atrial fibrillation

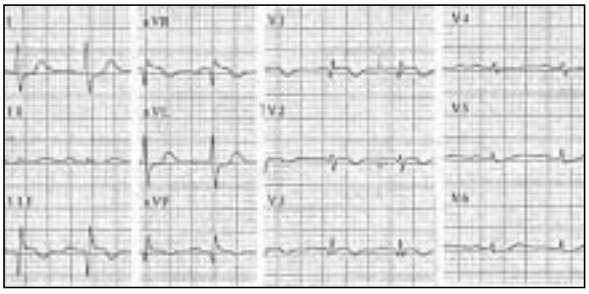

Figure 4. ECG in PE.

Chest Radiography

Chest radiography results are almost always negative in the very early fases. In few occasions is possible to see the Westmark Sign (dilatation of the pulmonary vessel proximal to the embolic obstruction) (Figure 5).

Late non specific and common findings include an elevated emidiaphragm, unilateral pleural effusion and platelike atelectasis (Figure 6).

The major utility of chest radiography is that to provide an alternative diagnosis (e.g. Pneumothorax).

Computed Tomographic Pulmonary Angiography (CTPA)

Computed tomographic pulmonary angiography (CTPA) is rapidly becoming the first line modality for imaging pulmonary embolism[9]. However, limitations for the accurate diagnosis of small peripheral emboli have prevented the unanimous acceptance of CT-

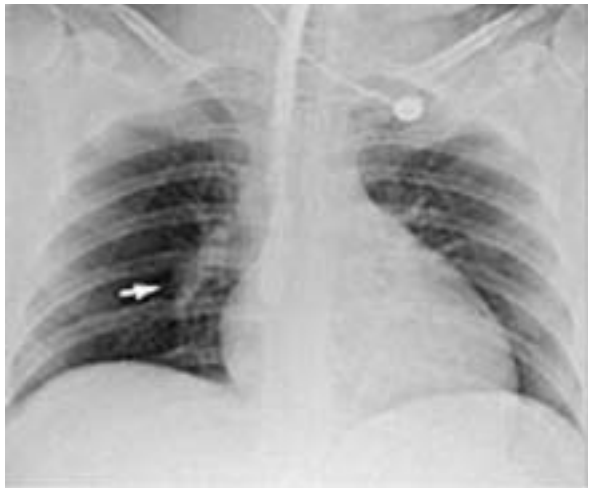

Figure 5. Westmark sign in PE.

PA as the new standard of reference for imaging PE although the actual significance of the detection and treatment of isolated peripheral emboli is uncertain. At the same time the high negative predictive value of CTPA for excluding clinically significant PE has been established in retrospective and prospective studies. The introduction of multidetector-row spiral CT (MDCT) has greatly improved visualization of peripheral pulmonary arteries and detection of small emboli. Previous concerns regarding the accuracy of spiral CT for the accurate diagnosis of peripheral pulmonary emboli should thus be overcome[10].

In summary, CTPA is now the recommended inizial lung imaging modality for PE. Patients with a good quality negative CTPA do not require further investigation or treatment for PE[8].

Echocardiography

Echocardiography is diagnostic in massive PE but allows a diagnosis in only a minority of others sub massive or peripheral PE. Although it can give prognostic information, it is of less value in predicting mortality than clinical features or the presence of acidosis[11]. Use of transoesophageal route improves diagnostic accuracy by more reliably demonstrating intrapulmonary and intracardiac thrombus and has been used during cardiopulmonary resuscitation, but other advantages over the trans thoracic approach are marginal and availability is limited.

Therapeutic Approach

The principal therapeutic approach to PE are summarized in Figure 7.

Key Points[8]

- Thrombolysis should NOT be used as first line treatment in non massive PE
- Otherwise thrombolisis *is the first line treatment in massive PE* and may be instituted on clinical grounds alone if cardiac arrest is imminent
- During ACLS in case of PE a 50 mg IV bolus of alteplase is reccommended
- Heparin should be given to patients with intermediate or high clinical probability before imaging
- Unfractioned heparin (UFH) should be considered as a first dose bolus, in massive PE or when a rapid reversal of effects may be needed
- Otherwise, low molecular weight heparin (LMWH) should be preferred to UHF, having equal efficacy and safety and being easier to use
- Oral anticoagulation should only be commenced once VTE has been reliably confirmed

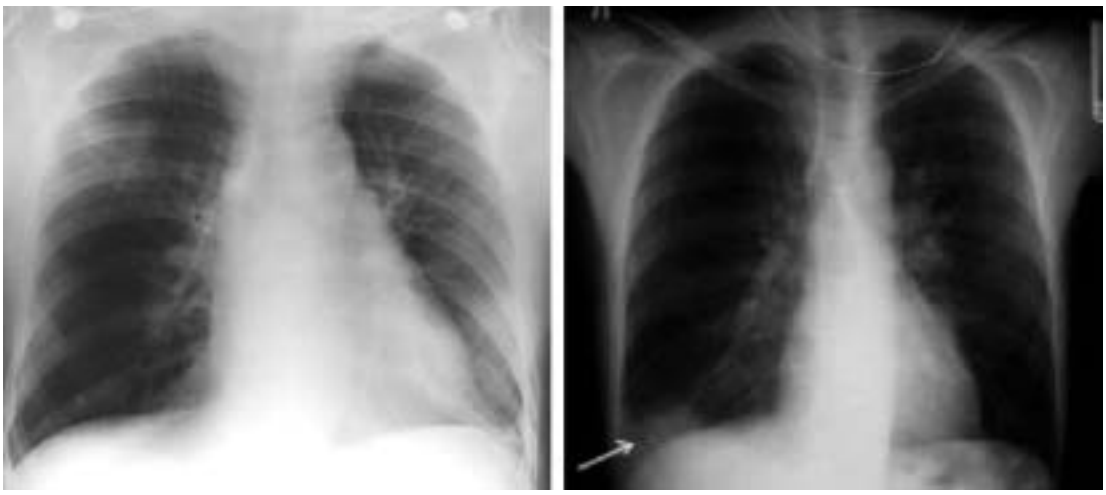

Figure 6. Late, non specific findings in PE.

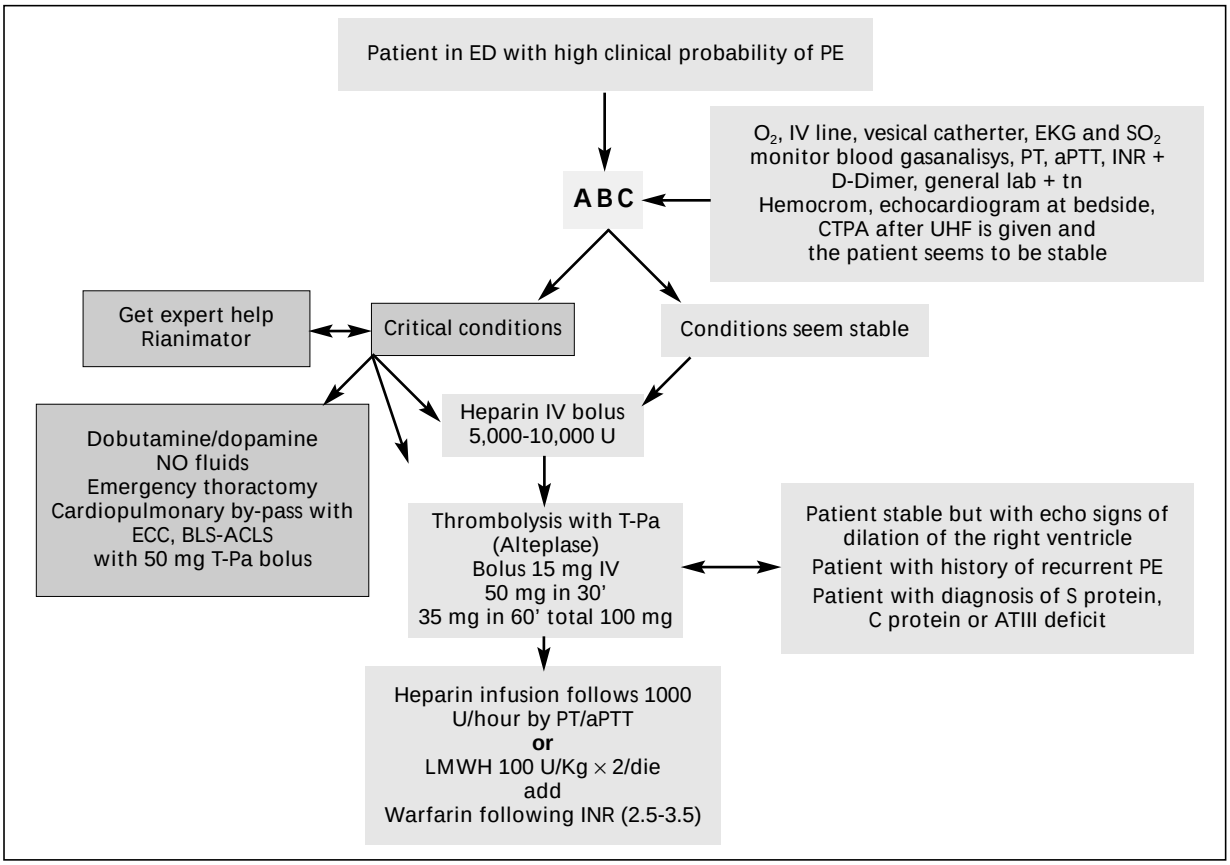

Figure 7. Guidelines for the management of PE in the Emergency Department.

- The target INR should be 2.5-3.5; when it is achieved heparin can be discontinued
- The standard duration of anticoagulation is: 4-6 weeks for temporary risk factors, 3 months for idiopatic first PE, 6 months in all other cases.
- CTPA is now the recommended lung imaging modality for PE.

An Open Window on the Future

The future of the therapeutical approach to PE may be in a hybrid treatment. Recent studies[12] used a combined approach to thrombolisis using mechanical fragmentation, localyzed fibrinolysis and clot aspiration. A conventional pigtail catheter for pulmonary angiography was used as fragmentation catheter system by rotating the catheter manually about the axis of the stationary guidewire and advanced or withdrawn over the guidewire as required.

After fragmentation all patients received an intrapulmonary injection of rt-PA (13 mg/h) followed by manual clot aspiraton using a large lumen PTCA guide catheter. All the patients survived the procedure and their clinical status improved and there was no recurrent pulmonary thromboembolism after the procedure.

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