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# Pathophysiology, Diagnosis and Treatment of Pulmonary Embolism Focusing on Thrombolysis - New approaches

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## 1. Introduction

### 1.1 Incidence and mortality of pulmonary embolism

Pulmonary embolism (PE) is not a disease by itself but may have a venous thrombotic source and is therefore more precise if classified as venous thromboembolism (VTE). According to the international registry, the frequency of VTE is 150-200 new cases diagnosed per 100,000 inhabitants per year. Out of this, one third is diagnosed as primary PE (Oger, 2000; Walther et al., 2009). Following the diagnosis the average mortality is 11% in the first two months (Goldhaber et al., 1999). In the ICOPER study, the total mortality of PE in the first 3 months was 17.5%. However, in the long run the recurrent embolic episodes and lack of revascularisation caused progressive pulmonary hypertension (Goldhaber et al., 1999). The mortality of untreated PE is 30% and with adequate treatment can be reduced to 2-8% (Goldhaber, 1998). The hospital mortality of haemodynamically stable PE patients is overall 10% in general, 4% in the first 24 hours (Kline et al., 2003). Mortality of PE with respiratory and cardiovascular failure on hospital admission can be up to 95%. Hospital mortality is 80% in patients requiring mechanical ventilation and 77% in those who need cardiopulmonary resuscitation in the first 24 hours (Janata et al., 2002). Only 29% of fatal PE cases (verified at hospital autopsies) were previously diagnosed clinically. Based on these facts, the primary goal in PE management is a rapid and clear diagnosis followed by the appropriate treatment (S. Büchner & Th. Hachenberg, 2005).

### 1.2 Etiology

The source of PE in majority of cases can be due to the postoperative state, trauma injury, long term immobilization causing deep vein thrombosis (DVT), or congenital/acquired coagulation defect (Goldhaber & Morrison, 2002; Schürmann et al., 1992; Spöhr et al., 2005; Tapon, 2008). There are congenitally predisposed and non-influenced factors in the aetiology of VTE. Most important ones are: old age, family predisposition, genetic defects -

activated protein C resistance (Dahlbäck, 1995), 20210A mutation of factor II (Poort et al., 1996), hyperhomocysteinaemia (den Heijer et al., 1996), antithrombin III, protein C and protein S deficiency (Demers et al., 1992).

Aetiology can be divided into two groups:

*a/ Congenital risk factors:* Lack of anti-thrombin III (0.2%), lack of protein C (0.8%), lack of protein S (1.3%), Leiden point-mutation of factor V (3.0%), mutation of prothrombin G20210 A (2.3%) (Ageno et al., 2006).

*b/ Acquired risk factors:* DVT, phlebitis, immobilization, bed rest, post-traumatic and operative state, sepsis, diabetes, smoking, hypovolaemia, diuretic treatment, elevated plasma/blood viscosity, coagulation disorders (disseminated intravascular coagulation, heparin induced thrombocytopenia (HIT), drug induced coagulopathy (anticoncipient, oestrogen), obesity, sedentary lifestyle, pregnancy, postnatal state, cardiac insufficiency, heart valve disorders, artificial valves, central venous catheter, pacemaker electrode, tumour, old age, nephrosis syndrome (Goldhaber et al., 1997).

### 1.3 Pathophysiology

Based on the occlusion of the pulmonary vasculature we can differentiate between mild: <25%, intermediate: 25-50% and severe: >50% PE types. The pathophysiology of PE runs on two parallel pathways:

- *haemodynamic alterations:* The oxygen demand and workload on the right atrium increases with the afterload, while cardiac index decreases (even with normal arterial blood pressure and tachycardia) leading to systemic hypotension. The right intraatrial pressure increases and the pressure gradient between the right atrium and the aorta drops, pushing the intraventricular septa into the cavity of the left ventricle (LV) (D-sign). A severe shock with global cardiac ischemia can develop.
- *hypoxaemia:* Ventilation/perfusion (V/Q) disequilibrium rises. Areas with hypoperfusion have an increased V/Q, while it decreases on hypoventilated (atelectasis) or normally perfused regions. Low LV cardiac output results from shunt-perfusion and hypoxaemia (Nowak et al., 2007). Platelet released vasoactive substances cause vaso- and bronchospasm in the affected regions (Stratmann & Gregory, 2003; Wood, 2002; Konstantinides, 2005). Surfactant production impairs in the early phase of pulmonary hypertension. Due to shunt-perfusion, global arterial hypoxaemia develops with a decrease of arterial oxygen saturation (Konstantinides & Hasenfuss, 2004).

#### 1.3.1 Risk stratification

Based on the haemodynamic symptoms, PE can be either *massive*, characterised by systolic blood pressure lower than 90 mmHg or a systolic blood pressure decrease > 40 mmHg, or *non-massive* which includes *submassive* severity characterised by increased right ventricular pressure (Torbicki et al., 2000).

The most recent PE guideline changed the definitions of various risk groups, according: high risk and non-high risk categories.

*High risk definition:* Shock and/or hypotension (systolic blood pressure <90 mmHg or a drop in blood pressure greater than 40 mmHg within 15 min. excluding other causes of shock (e.g. arrhythmia, hypovolaemia, sepsis etc.).

All others can be listed under *non-high risk* PE. Based on right ventricular (RV) pressure overload and myocardial injury, we can differentiate a subgroup, the *intermediate risk* PE patients without shock.

Mortality risk		Risk markers			
		shock/hypotension	RV dysfunction	Myocardial injury	Potential treatment
High >15%		+	(+)	(+)	Thrombolysis or embolectomy
Non high	Intermediate 3-15%	-	+	+	Hospital admission
			+	-	
	-	-	-		
	Low <1%	-	-	-	Early discharge or home treatment

(+) Presence of shock/hypotension it is not necessary confirm RV dysfunction

Table 1. Risk stratification according to the ESC 2008 guidelines.

The prognosis of the increased RV pressure (intermediate risk) group is worse than the normal RV pressure group (Torbicki et al., 2008).

The clinical probability of pulmonary embolism in outpatients (Wells et al., 2001)	Score
<i>Clinical signs</i>	
Deep vein thrombosis (DVT)	+3.0
Pulmonary embolism (PE) suspected from other signs or symptoms	+3.0
Hearth rate >100 / min	+1.5
Operation, immobilization, bed rest in the last 4 weeks	+1.5
Former DVT or PE	+1.5
Hemoptysis	+1.0
Malignancy (active or confirmed in the last 6 months)	+1.0
<i>Probability of PE</i>	
Small	< 2.0
Medium	2.0-6.0
High	> 6.0

Table 2. Clinical probability score

### 1.4 Pulmonary embolism diagnostic strategy

Acute PE, in the presence of shock/hypotension, RV dysfunction and myocardial injury causes high mortality risk. Rapid and clear diagnosis and appropriate therapy may help to improve survival of this critical condition.

#### 1.4.1 Physical signs of PE

In the presence of typical physical signs (dyspnoea, chest pain, syncope, tachypnea, tachycardia, cough, hemoptysis, signs of DVT, cyanosis, etc.) the diagnosis of PE is 90% reliable, although the severity of symptoms do not correlate with the actual illness. About 10% of high-risk cases are recognised by radiology imaging and considered to be non-high risk according to physical symptoms.

Physical signs and symptoms: severe stabbing chest pain (52%), tachycardia (26%), cough (20%), cyanosis (15%) or paleness, increased perspiration, fever (38.5%), dyspnoea (with acute onset 80%), tachypnea (70%), hemoptysis (11%), mortal fear, syncope (19%), low blood pressure, haemodynamic failure with large vessel obstruction, arrhythmia (atrial or ventricular extrasystole, acute atrial fibrillation, flutter, etc.) (Miniati, Prediletto, Formichi, Marini, Di Ricco, Tonelli, Allesscia & Pistolesi, 1999a; Stein & Henry, 1997).

#### 1.4.2 Chest X-ray

According to the PISAPED study, occlusion of the hilar artery, oligoemia, wedge shaped infiltration against the pleural wall is detectable in 15-45% of all cases (Miniati, Prediletto, Formichi, Marini, Di Ricco, Tonelli, Allesscia & Pistolesi, 1999b). In acute PE the typical X-ray signs can be weak or absent, but a single-sided elevation of the diaphragm, stripe-like atelectasis and the oedema of the affected pulmonary tissue (Westermarck-sign) may develop with the prominence of the pulmonary artery. Occasionally unilateral pleural effusion is present. Chest X-ray is useful to exclude certain diagnoses.

#### 1.4.3 Electrocardiography (ECG)

The most common alterations are: sinus tachycardia,  $S_1Q_3T_3$  waveform (McGinn-White syndrome), acute P-pulmonale, negative T waves in  $V_{1-3}$  leads, incomplete or complete right bundle branch block, signs of RV strain, acute atrial fibrillation, atrio-ventricular conduction failures. Enlarged  $S_I S_{II} S_{III}$  waveform develops after the dilatation of the right cavities causing the rotation of the cardiac axis. ECG signs are positive only in 50% of all patients (Torbicki et al., 2000; Torbicki et al., 2008; Geibel et al., 2005; Rodger, Makropoulos, et al., 2000).

#### 1.4.4. Perfusion scintigraphy

Multiple studies have confirmed the benefit of perfusion scintigraphy as a non-invasive diagnostic procedure. It is necessary to combine perfusion scintigraphy with additional radiology imaging, like ventilation scintigraphy or chest X-ray. Various studies have confirmed that ventilation-perfusion scintigraphy has a positive predictive value of 88% (The PIOPED Investigators, 1990; Lee et al., 2005). The PISAPED study divided the probability of PE into 3 groups based on chest X-ray and perfusion scintigraphy results (Miniati et al., 1996). The sensitivity of perfusion scintigraphy is 92% with a positive predictive value of 92%. It has a negative predictive value of 88% with the specificity of 87%. Chronic pulmonary diseases caused perfusion defects may produce PE characteristic false results. To sum up, scintigraphy can help to exclude PE (error rate: 0.9%, confidence interval: 2.3%) (Kruip et al., 2003).

#### 1.4.5 Angiography

According to the most recent PE guideline, the use of angiography is questionable as an invasive and hazardous intervention with mortality rate of 0.2%. The use of angiography is

recommended in case of uncertain radiological imaging results. Non-invasive CT angiography offers comparable or better sensitivity (Wan et al., 2004; Agnelli et al., 2002).

#### 1.4.6 Computed tomography, multidetector computed tomography (MDCT)

The MDCT is a non-invasive approach, replacing angiography without the need of central venous access. It has a sensitivity of 83% and specificity of 96%. The negative predictive value of MDCT for PE is 89% in the intermediate and 96% in the low clinical risk groups. The cost-benefit and cost-life ratio increases significantly with the combination of MDCT and D-dimer assessment (Perrier et al., 2004; van Belle et al., 2006). With MDCT imaging one can visualise pulmonary vasculature up to the segmental level. An MDCT result showing a PE up to the segmental level could be taken as firm evidence (Eyer et al., 2005; Brunot et al., 2005; Righini et al., 2008; Ghaye et al., 2001; Perrier et al., 2004).

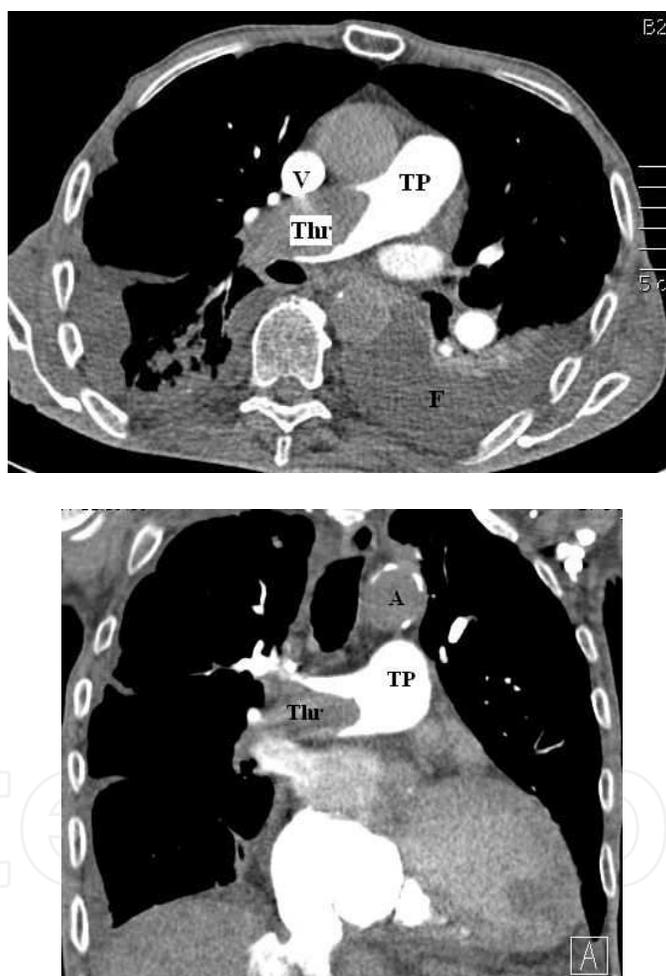


Fig. 1. Computed tomography image of acute pulmonary embolism. (From authors own collection. A: aorta, TP: pulmonary trunk, F: thoracic effusion, Thr: clot)

#### 1.4.7 Echocardiography

##### *Transthoracic echocardiography*

Echocardiography is a useful bedside non-invasive procedure in the differential diagnosis of various conditions (acute myocardial infarction, aortic dissection, pericardial tamponade,

chest pain, valve dysfunction, hypovolaemia). The sensitivity of echocardiography is about 60-70% in PE. Negative results do not exclude PE. Acute massive PE has characteristic echocardiography signs: RV hypokinesis and/or dilatation, the end diastolic diameter of the RV in the parasternal short axis > 30 mm, or RV/LV end diastolic diameter ratio > 0.9, in the apical or subcostal axis, D-sign, increased pulmonary arterial pressure, dilatation of the inferior caval vein. A heart cavity thrombus, patent foramen ovale (with the risk of paradox thrombi), tricuspidal valve thrombosis or vegetation and floating clot in the right ventricle can also be visualised.

The positive echocardiographic result has a predictive value in haemodynamically stable patient, as the intermediate risk group has worse outcome (Konstantinides, 2008; Torbicki et al., 2003; Ferrari et al., 2005; Hsiao et al., 2006; Casazza et al., 2005; Bova et al., 2003; Miniati et al., 2001; Roy et al., 2005; Konstantinides et al., 1998).

#### *Transoesophageal echocardiography*

The transoesophageal echocardiography is a semi-invasive diagnostic procedure, which can be useful in mechanically ventilated patients. Benefits of the transoesophageal approach are: visualisation of thrombi in the pulmonary trunk and/or main pulmonary arteries and also in the caval vein. Possible tumours originating from the heart or floating into the cavities of the heart can also be visualised (Sanchez et al., 2008).

#### **1.4.8 The diagnosis of DVT**

With duplex ultrasound the clot is visible as a hyperechogenic signal. The procedure has 95-98% specificity. The sensitivity for PE is rather low, only 30-50% of PE cases present DVT with ultrasonography (Lee et al., 2005). The only validated verification method is the incomplete compressibility of the vein indicating the presence of the clot (Goldhaber & Morrison, 2002; Lee et al., 2005; Le Gal et al., 2006).

Although extremity CT can also aid the diagnosis of DVT, the increased irradiation, need of contrast agent and elevated costs contraindicate the use of CT scan in all cases (Brenner & Hall, 2007).

#### **1.4.9 Laboratory diagnostics**

*Arterial blood gas analysis:* Hypocapnia with hypoxaemia is characteristic for PE. About 20% of patients have a normal arterial oxygen tension and normal alveolar-arterial oxygen gradient (Rodger, Carrier, et al., 2000; Stein et al., 1996).

*D-dimer* is a fibrin degradation product. Quantitative ELISA or ELISA-like methods are 99% sensitive, if D-dimer concentration is above 500 µg/l. According to Dunn et al. the sensitivity for PE is 96.4%, with a negative predictive value of 99.6%, specificity 52.0% and positive predictive value 9.5%. Although the measurement is specific for fibrin, but the specificity of fibrin for VTE is considerably lower, the summarized specificity is only 40-65%. The D-dimer test can be positive in the following diseases: infections, tumours, necrosis, pregnancy, postnatal, postoperative state, sepsis, etc., therefore, it cannot be used generally. In emergency situations, the D-dimer test is useful to exclude PE from differential diagnosis. Segal recommended the inclusion of D-dimer into the Geneva and Wells score systems (Dunn et al., 2002; Segal, Eng, et al., 2007; Spannagl et al., 2005; Reber et al., 2004; van Belle et al., 2006).

*Cardiac troponin T and B-type natriuretic peptide (BNP):* Increased cardiac troponin and BNP levels are good indicators of impaired RV function. About 11-50% of PE patients show

increased marker levels. Echocardiography results correlate showing a decreased RV function. Negative troponin results are good predictors of favourable outcome. Both markers are useful and independent predictors of the 30 days mortality. Impaired RV function with increased troponin and BNP are relative indications of thrombolysis (TL) therapy in the intermediate risk group (Giannitsis et al., 2000; Kostrubiec et al., 2005; Krüger et al., 2004; ten Wolde et al., 2004; Worth, 2009). The recommended therapeutic approach according to Kucher and Goldhaber based on these data (Kucher & Goldhaber, 2003):

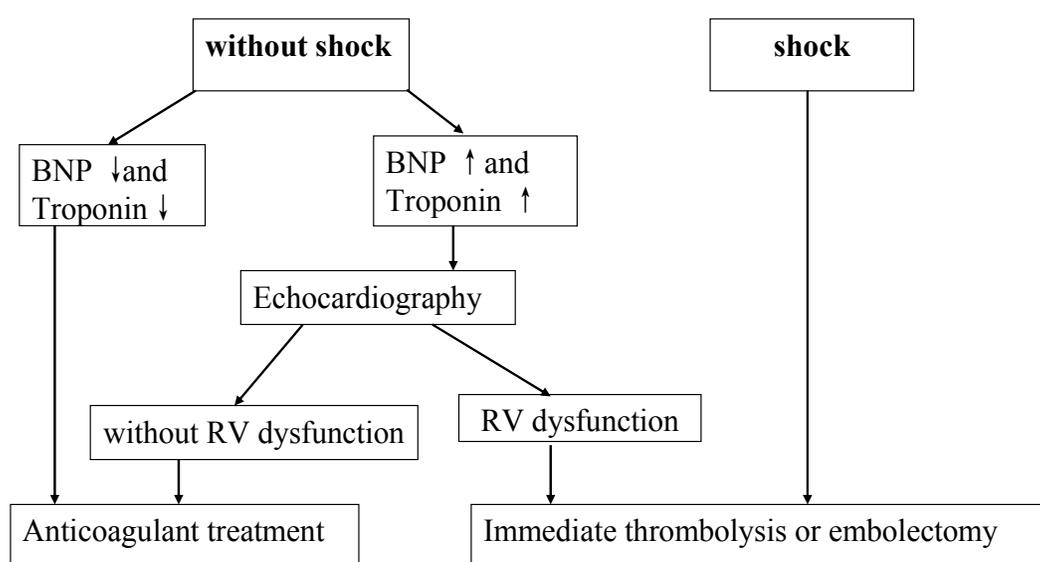


Fig. 2. Kucher and Goldhaber recommendation for the treatment of pulmonary embolism based on biomarkers and echocardiography.

Cases with severe haemodynamic shock present elevated lactate and metabolic acidosis due to global microcirculatory impairment and tissue hypoxaemia. These markers can predict poor outcome.

According to the recent guidelines, the diagnosis of PE is mainly based on the results of echocardiography, MDCT and biomarkers (Torbicki et al., 2008).

## 1.5 Therapy

### 1.5.1 Acute therapy

For main therapeutic recommendations, we follow the ESC 2008 guidelines (Torbicki et al., 2008). Anticoagulation therapy should be initiated upon suspicion of PE. 5000 IU Na-heparin is recommended as intravenous bolus if the patient had not already received Low Molecular Weight Heparin (LMWH) previously. Besides providing secure venous access, patients should receive immediate oxygen therapy through a 50% or 100% face mask. The indication of oxygen therapy is absolute, but mechanical ventilation should be used with caution. Mechanical ventilation may decrease the venous reflow and increases RV insufficiency, therefore, low tidal volume (7 ml/kg) ventilation and intravenous fluid therapy is recommended. The alveolar-arterial gas exchange can also be impaired as shunt-flow and cardiac output decrease (Singer, M; Webb, 2004; Sevransky et al., 2004). Capnometry is highly recommended during mechanical ventilation, as it may change due to thrombolysis

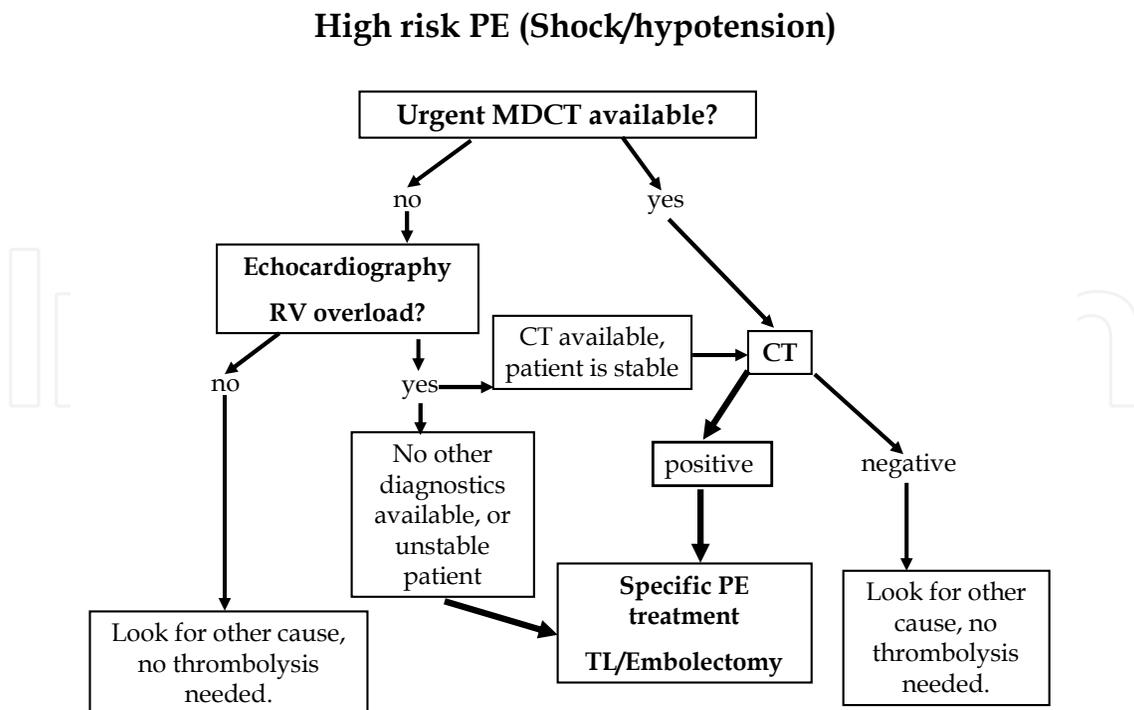


Fig. 3. The ESC 2008 guideline recommended diagnostic steps for high risk PE patients

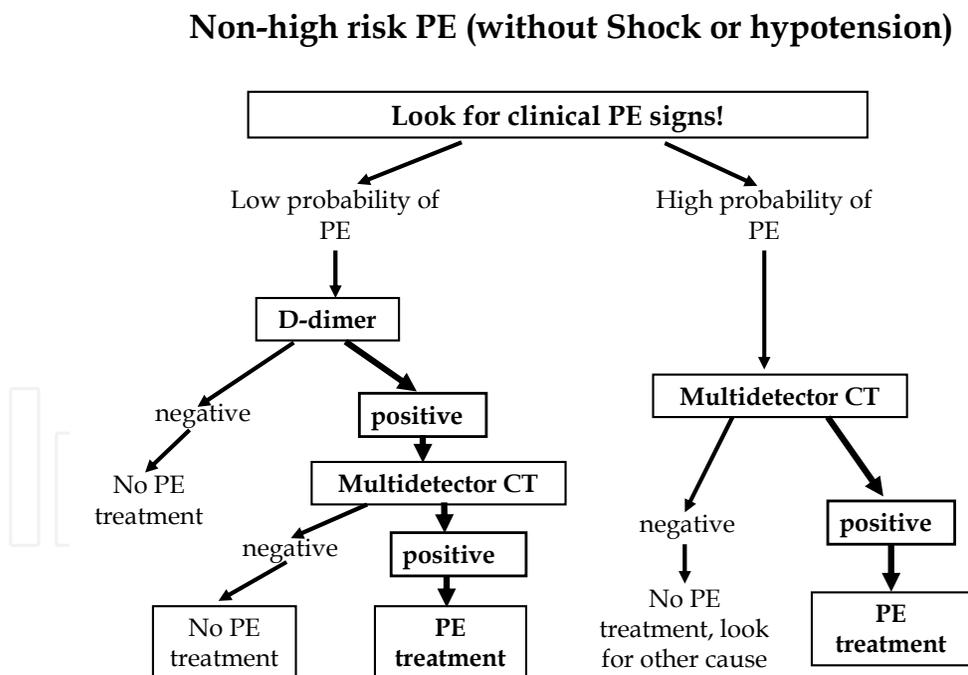


Fig. 4. The ESC 2008 guideline recommended diagnostic steps for non-high risk PE patients

or re-embolism. Morphine (or other opiate analgesic) can be administered as repeated intravenous bolus of 2 mg for analgesia. To achieve optimal haemorheological parameters and a desirable volume state, aggressive fluid resuscitation must be carried out intravenously in the acute phase (crystalloid 1.5-2 ml/kg/h). Early fluid resuscitation is recommended based on hypotension from the loss of LV end diastolic volume. Ozier et al.

measured the effect of 600 ml crystalloid infusion and found an increase of cardiac index from 1.7 to 2.0 l/min/m<sup>2</sup>. Also, Mercat et al. found the same increase of cardiac index after the infusion of 500 ml dextrane. Modest fluid challenge is recommended, as fluid overload may depress contractility and decrease cardiac output (Kasper et al., 1997; Mercat et al., 1999; Ozier et al., 1984). If bronchospasm develops 200 mg intravenous theophyllin may be administered. If required, norepinephrine and/or dobutamine are the choice of positive inotropic drugs. Norepinephrine improve RV function with direct effect on contractility (Prewitt, 1990). Büchner primary recommends norepinephrine and dobutamine combination for haemodynamic shock (S. Büchner & Th. Hachenberg, 2005).

Elevated lactate levels indicate capillary perfusion impairment. The normalisation of lactate shows the resolution of the haemodynamic failure. Also, a radial arterial line is useful for continuous blood pressure monitoring and to draw frequent blood samples upon the verification of high-risk or non high-risk PE. Pulse contour cardiac output systems, like the "PiCCO"-system (Pulsion Medical Inc., Germany) is capable of continuous haemodynamic monitoring including cardiac output. Phosphodiesterase-III inhibitors (i.e. enoximon) and Ca-channel sensitizers (i.e. levosimendan) may have a beneficial effect, but insufficient clinical evidence is available yet (Nowak et al., 2007; Kerbaul et al., 2007). Also, the inhalation of nitrous oxide may improve the gas exchange of patients with PE (Torbicki et al., 2008).

If deep vein Doppler ultrasound suspects a floating, weak structure clot, thus re-embolisation may occur, a temporary placement of caval vein filter should be considered before TL.

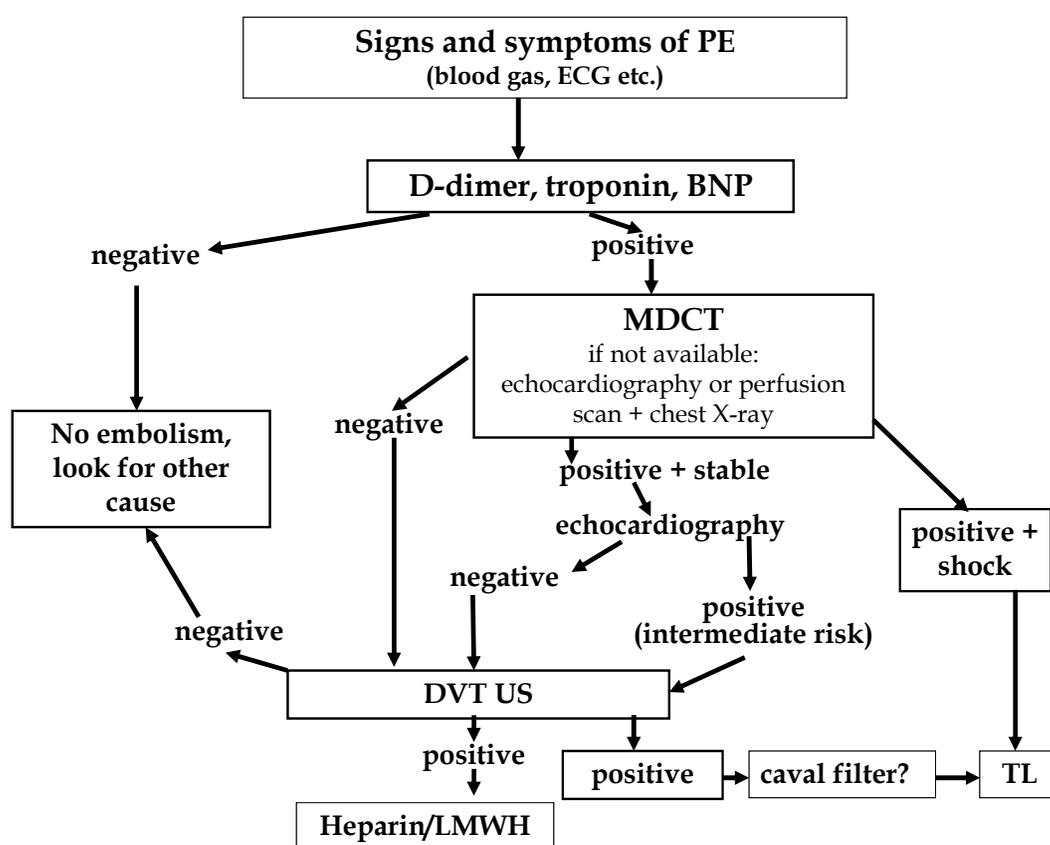


Fig. 5. The authors' own diagnostic and therapeutic approach (US: ultrasound)

### 1.5.2 Thrombolysis

Based on this complex classification a planned approach is essential. The aim of the management of acute severe PE is the resolution of the pulmonary artery obstruction. The most common procedure is TL, but invasive radiology procedures (clot fragmentation and vacuum evacuation, or selective TL through catheter arteriography, Class IIb C) or acute surgical embolectomy (Class I C) can also remove PE.

In critical patients with severe shock and confirmed PE the indication of urgent systemic TL is absolute (Class I A). The recommended medications and appropriate dosage is available in the current PE guideline (Table 3). The authors support the accelerated TL (rt-PA or SK) protocol in haemodynamically instable patients. According to our experience the ultra-high dose streptokinase is an economically reasonable and effective alternative to rt-PA (Sárosi et al., 1997; Sárosi et al., 1995).

Medication	Continuous TL	Accelerated TL
streptokinase (SK)	250,000 IU/30 min, following 100,000 IU/h for 12-24 hours	1.5 IU/2 hours
urokinase (UK)	4,400 IU/kg/10 min, following 4,400 IU/kg/h for 12-24 hours	3 IU/2 hours
rt-PA	100 mg/2 hours	0.6 mg/kg/15 min (max: 50 mg)

Table 3. Recommended thrombolytic regimens (Torbicki et al., 2008)

In the intermediate-risk group, with main arterial embolism and increased RV load, positive D-sign, elevated troponin and BNP levels but without haemodynamical impairment, TL is recommended only after considering relative contraindications and acquisition of written informed consent (Class IIb B).

Certain patient history *absolutely contraindicates TL*: haemorrhagic stroke, or stroke of unconfirmed origin, ischemic stroke in the last 6 months, central nervous system tumour, neuro, trauma, or general surgery intervention in the last 3 weeks, gastrointestinal bleeding in the last 30 days, known bleeding, or bleeding disorder.

The *relative contraindications* are: transient ischemic attack in the last 6 months, oral anticoagulation (vitamin K antagonists), pregnancy and the 1<sup>st</sup> week following labour, organ biopsy and non-compressible puncture, traumatic resuscitation, critical hypertension (RR<sub>s</sub> > 180 mmHg), advanced liver disease, infective endocarditis, active peptic ulcer (Torbicki et al., 2008). In life-threatening situations, every contraindication can be considered to be relative.

The effectiveness of TL should be controlled between 12 and 24 hours by a second look MDCT or other available diagnostic procedure (perfusion lung scan or echocardiography). If the decrease of unperfused area does not improve by 30% following the first treatment cycle, TL should be repeated after 24 hours.

During *resuscitation*, chest compressions assist the mechanical fragmentation of clot and improve the infiltration of drugs into the clot. Urokinase 2-3 MIU, rt-PA 2 × 50 mg or streptokinase 1.5 MIU (may repeat once after 15 minutes) can be used for TL. Compressions should continue for at least 90 minutes during TL. As TL is beneficial in PE and also in acute myocardial infarction, no firm diagnostic evidence is needed for the treatment (Böttiger & Spöhr, 2003). One main advantage of TL is the possibility of prompt use and that it may improve overall microcirculation (Böttiger & Martin, 2001).

Based on our previous clinical investigations, in case of bleeding complications the repetitive measurement of clot formation factors (namely fibrinogen and plasminogen) may indicate the need of specific factor replacement or fresh frozen plasma infusion during or following TL. Major bleeding complications can be reduced below 5%, if factor replacement takes place in patients with fibrinogen levels below 1.5 g/l accompanied by minor bleeding disorder or fibrinogen levels < 0.6 g/l (Mühl et al., 2007).

Patients may not benefit from the TL of a more than 5-7 days old clot. Also, a second unsuccessful TL may indicate the presence of an older, connective tissue rich clot. Invasive radiology clot fragmentation and removal with or without selective TL should be used in these scenarios.

*Anticoagulation therapy during TL:* In the rt-PA group unfractionated heparin is recommended during TL (500-1000 IU/h, based on actual partial thromboplastin time (aPTT) levels on admission) (Segal, Streiff, et al., 2007).

*Anticoagulation therapy after TL:* Anticoagulant therapy starts after strepto- or urokinase TL with intravenous unfractionated heparin to maintain aPTT (check every 4 hours!) between 50-70 seconds for the first 48 hours and continues with a therapeutic dose of LMWH, if no further TL cycle is necessary. Using the "Heparin adjustment nomogram", the dose of Na-heparin is adjusted to reach a target aPTT (Torbicki et al., 2008).

Anticoagulant therapy should be provided with intravenous unfractionated heparin to maintain the aPTT between 60-70 seconds for 48 hours. If TL was effective it should be continued with a therapeutic dose of LMWH. Following TL, long term anticoagulation (acenocoumarol or warfarin) can start on day 3 or 4 (Torbicki et al., 2008; Kearon et al., 2008).

In case of unfractionated heparin use, the incidence of HIT is 1-3% (about 1% with LMWH), therefore regular platelet count check is recommended (Greinacher, 2009; Morris et al., 2007). In case of confirmed HIT, one should switch from heparin/LMWH therapy to: hirudin, lepirudin, danaparoid or fondaparinux.

One of the most common complication of TL is minor bleeding (arterial/venous port bleeding, haematuria, suffusions, e.t.c.), major bleeding occurs in 13% of cases. The incidence of intracranial haemorrhage is 1.8% (Spöhr et al., 2005), (Konstantinides et al., 2002; Goldhaber et al., 1993).

### **1.5.3 Catheter extraction and surgical embolectomy**

Indications of percutaneous catheter embolectomy and fragmentation are unsuccessful systemic TL, contraindications of systemic lysis, PE with haemodynamic shock (resuscitation, mechanical ventilation), clot in the right heart, and also an alternative for the surgical embolectomy if no experienced team is available (Kucher et al., 2005; Uflacker, 2001).

Surgical embolectomy has a high mortality rate in the high-risk PE group. Indications are narrow, only patients with absolute systemic TL contraindications and in the absence of consent for TL may benefit from surgical intervention (Meneveau et al., 2006). Previous unsuccessful TL is not a contraindication for surgical embolectomy (Aklog et al., 2002).

### **1.5.4 Intravenous (caval) filter**

Statistically there is no firm evidence of improved 12 days mortality of the caval filter use. Transient caval filters may be used up to 14 days. Late complications include migration and device thrombosis. Indications are not general; the main indication is suspected

reoccurrence of PE and contraindication of long-term anticoagulation (Hann & Streiff, 2005). Also, venous filters for PE prophylaxis may be beneficial in trauma patients, but further studies are required to draw firm clinical evidence (Rajasekhar et al., 2011).

### **1.5.5 Follow-up after PE therapy**

Following PE therapy, a switch from heparin/LMWH to oral anticoagulation is recommended. Oral anticoagulation should be continued for 6 months. Following, an extended diagnostic procedure should take place to elucidate possible genetic factors or acquired thrombophilia behind the development of PE. In case of irreversible complications or positive thrombotic predisposition, continuous oral anticoagulation is needed (Kearon et al., 2008).

## **2. A new approach to PE**

### **2.1 The role of matrix metalloproteinases**

Experimental evidence indicated that the pathophysiology of PE implies the activation of matrix metalloproteinases (MMPs) (Uzuelli et al., 2008; Dias-Junior et al., 2009; Souza-Costa et al., 2005; Souza-Costa et al., 2007; Palei et al., 2005; Fortuna et al., 2007). Indeed, hemodynamic derangements associated with this condition improved with the inhibition of MMPs. Neutrophil activation (Eagleton et al., 2002) and rapid release of granules containing large amounts of MMP-9 in inflammation (Van den Steen et al., 2002) and during PE explains how MMPs, especially MMP-9, are involved in pathophysiology of PE. The increased activity and levels of MMP-9 found in ischemic stroke, or the upregulation of the enzyme after cerebral ischemia are interestingly similar to PE (Asahi et al., 2000). The degradation of type IV collagen, laminin, and fibronectin by MMP-9, may contribute to hemorrhagic transformation after cardioembolic stroke as these components are the main structure of the vascular matrix (Rosell et al., 2008; Montaner et al., 2001). Also, tissue plasminogen activator (or alteplase) can amplify MMP-9 levels by upregulation, thus increasing ischemic brain damage (Wang et al., 2004; Burggraf et al., 2007; Ning et al., 2006; Tsuji et al., 2005). There is evidence, that increased plasmin concentration may activate MMPs. Previous experimental work by our group aimed to assess the levels of MMPs following fibrinolysis for acute PE. Circulating levels of MMPs were measured serially (MMP-9 and MMP-2). Their endogenous inhibitors, tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 were also measured in alteplase and in ultra-high dose streptokinase-treated patients with acute PE (Mühl et al., 2010).

### **2.2 Measurements and discussion of TIMP/MMP changes in PE**

In our study MMP levels were assessed by sodium-dodecil-sulphate polyacrylamide gel electrophoresis, TIMP levels were measured with a commercially available ELISA kit (Mühl et al., 2010). Significant increases in pro-MMP-9 concentrations were found after TL therapy in both groups, but these were not associated with significant alterations in TIMP-1 levels. Pro-MMP-9/TIMP-1 ratio increased significantly. Interestingly, earlier increases in pro-MMP-9 levels and in pro-MMP-9/TIMP-1 ratio were found in subjects treated with streptokinase. From the 3<sup>rd</sup> day pro-MMP-9 levels and pro-MMP-9/TIMP-1 ratio returned to normal. No significant changes in pro-MMP-2 concentrations were measured after TL. Moreover, we found no significant changes in TIMP-2 concentrations or in pro-MMP-2/TIMP-2 ratio.

Although there is a lack of firm evidence, the possible explanation for increased MMP-9 levels during treatment with alteplase is the promotion of MMP-9 release by neutrophils (Cuadrado et al., 2008). According to our knowledge, no previous study has reported that streptokinase induces the release of MMP-9.

A slower increase of pro-MMP-9 was found in alteplase treated patients, but the precise explanation for this difference between fibrinolytic agents is not yet elucidated. There is significant interindividual variability in neutrophil degranulation (Cuadrado et al., 2008), therefore a multi-central study may draw firm evidence on this question.

No definitive conclusion can be drawn yet, but it is widely acknowledged that intracerebral hemorrhage is the most feared bleeding complication of TL (Arcasoy & Kreit, 1999). The use of alteplase enhanced MMP-9 levels, which has already been widely associated with hemorrhagic transformation after cardioembolic stroke (Rosell et al., 2008; Montaner et al., 2001). This observation offers an explanation for the hemorrhagic transformation during stroke.

It is possible that the MMP inhibitors may decrease the risk of intracerebral hemorrhage or other bleeding complication of TL for acute PE (Murata et al., 2008; Sumii & Lo, 2002; Machado et al., 2009) and may have beneficial hemodynamic effects (Fortuna et al., 2007; Palei et al., 2005).

### 3. Summary

Following risk stratification, prompt and specific diagnostics are life-saving in acute PE. Recommended diagnostic tools are biomarkers, MDCT and electrocardiography. Systemic TL is the first choice for high-risk PE patients, in case of contraindications surgical embolectomy or catheter clot fragmentation/removal should be considered. The fast resolution of haemodynamic shock indicates accelerated protocol systemic TL (rt-PA, SK or UK), as continuous TL dissolve clot slower and have a higher risk of bleeding disorder. The regular control of fibrinogen and plasminogen during and after TL, and clot formation factor supplement can reduce bleeding complications.

There is emerging evidence of the hypothesized role of the TIMP/MMP system in the development of bleeding complication. In future, pharmacological approach to MMP inhibition in human medicine may decrease the incidence of bleeding complications of TL.

### 4. References

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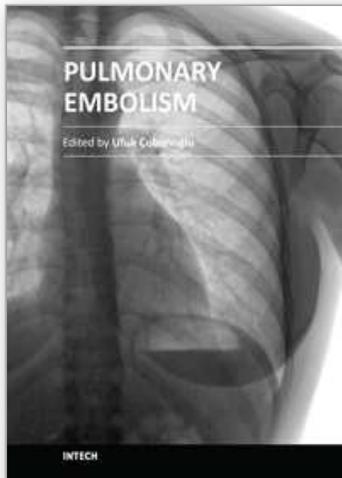
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## **Pulmonary Embolism**

Edited by Dr. Ufuk Çobanoğlu

ISBN 978-953-51-0233-5

Hard cover, 236 pages

**Publisher** InTech

**Published online** 14, March, 2012

**Published in print edition** March, 2012

Pulmonary embolism is a serious, potentially life-threatening cardiopulmonary disease that occurs due to partial or total obstruction of the pulmonary arterial bed. Recently, new improvement occurred in the diagnosis and treatment of the disease. The aim of this disease is to re-review pulmonary embolism in the light of new developments. In this book, in addition to risk factors causing pulmonary embolus, a guide for systematic approaches to lead the risk stratification for decision making is also presented. In order to provide a maximum length of active life and continuation of functional abilities as the aim of new interventional gerontology, the risk factors causing pulmonary embolus in elderly individuals are evaluated, and the approach to prevention and treatment are defined. The risk of the development of deep vein thrombosis and pulmonary embolism, combined with obesity due to immobility, the disease of this era, irregular and excessive eating, and treatment management are highlighted. Non-thrombotic pulmonary emboli are also covered and an attempt is made to constitute an awareness of this picture that can change the treatment and prognosis of the disease to a considerable extent. In addition to the pathophysiological definition of pulmonary embolus, the priority goal of quick and definitive diagnosis is emphasized, and diagnostic strategies are discussed in the book. A numerical analysis of the vena cava filters, which is a current approach to prevent pulmonary emboli recurrences, is presented in the last chapter.

### **How to reference**

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Diana Mühl, Gábor Woth, Tamás Kiss, Subhamay Ghosh and Jose E. Tanus-Santos (2012). Pathophysiology, Diagnosis and Treatment of Pulmonary Embolism Focusing on Thrombolysis - New approaches, Pulmonary Embolism, Dr. Ufuk Çobanoğlu (Ed.), ISBN: 978-953-51-0233-5, InTech, Available from:

<http://www.intechopen.com/books/pulmonary-embolism/pathophysiology-diagnosis-and-treatment-of-pulmonary-embolism-focusing-on-thrombolysis-new-approache>

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