Management of pulmonary embolism patients in the emergency department setting

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MANAGEMENT OF PULMONARY EMBOLISM PATIENTS IN THE EMERGENCY DEPARTMENT SETTING

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Abbreviations

CT – Computed Tomography

DOAC – Direct Acting Oral Anticoagulants

DVT - Deep Venous Thrombosis

HIT – Heparin Induced Thrombocytopenia

LMWH - Low Molecular Weight Heparin

LV – Left Ventricle

MDCT - Multiple Detector Computed Tomography

NOAC – Novel Oral Anticoagulants

PE - Pulmonary Embolism

PFO – Patent Foramen Ovale

RV – Right ventricle

t-PA – Tissue Plasminogen Activator

UFH - Unfractionated Heparin

VKA – Vitamin K Antagonist

VTE - Venous Thromboembolism

Table of Contents

1. Abstract

Title: Management of pulmonary embolism patients in the emergency department setting.

Name: Kim André Brevik

Key words: Pulmonary embolism; anticoagulation; venous thrombosis

Pulmonary embolism (PE) is a potential fatal disorder. It is the blockage of one of the pulmonary arteries in the lungs. In most cases, blood clots are the reason for the block and often, more than one clot is involved in causing the block. The clot often originates from the deep veins of the lower limbs, a condition known as deep venous thrombosis (DVT).

The most common clinical manifestations in PE includes sudden onset dyspnea, tachypnea, pleuritic chest pain, cough and hemoptysis. Clinical findings that should raise the suspicion to PE are, lower leg pain or swelling, pleuritic chest pain, dyspnea and elevated D-dimers on blood tests (although not very specific for the disease, but a negative D-dimer would virtually exclude PE as a likely diagnosis).

The challenge for the doctors working in the emergency room, can be to recognize the clinical presentation of a PE, as the symptoms often are non-specific. Unrecognized PE can potentially have fatal effects for the patient. The treatment is aimed at keeping the clot from becoming bigger and prevention of new clot formation. The mainstay of treatment of PE is anticoagulation whereas the most commonly used are heparin subcutaneous or intravenous, oral anticoagulants (warfarin) and new oral anticoagulants (NOAC). This is why recognition, combined assessment and intervention is of utter importance for the overall outcome.

2. Sažetak

Naslov: Obrada i liječenje bolesnika s plućnom embolijom u odjelu hitne medicine

Ime: Kim André Brevik

Ključne riječi: Plućna embolija; antikoagulansi; venska tromboza

Plućna embolija (PE) je potencijalno smrtonosna bolest uzrokovan blokadom protoka kroz jednu ili više plućnih arterija. U većini slučajeva PE ugrušak dolazi iz dubokih vena nogu, odnosno posljedica je duboke venske tromboze (DVT).

Najčešće manifestacije PE jesu: dispneja, tahipneja, pleuralna bol, kašalj i hemoptiza. Klinički nalazi koju podupiru sumnju na PE su oticanje ili bol u nogama, pleuralna bol, dispneja i povišeni D-dimeri u krvi (iako nespecifični, negativni D-dimeri isključuju PE kao moguću dijagnozu).

Često nespecifični simptomi pri prvoj prezentaciji bolesnika s PE izazov su za liječnike u hitnoj službi. Neprepoznata PE potencijalno je fatalna za bolesnika. Cilj liječenja je prevencija povećanja ugruška i prevencija formiranja novih ugrušaka. Osnova za liječenje PE je antikoagulantna terapija. Najčešće se koriste supkutani ili intravenski heparin, oralni antikoagulansi poput varfarina ili novi oralni antikoagulansi (*eng.* new oral anticoagulants - NOAC). Pravovremeno prepoznavanje, kombinirana procjena i timsko liječenje od ključnog su značenja za ukupan ishod bolesti.

3. Introduction

Pulmonary embolism (PE) is a disease affecting the lungs and its oxygen diffusion. The disease is caused by a clot formation in the lower limb, or rarely, other parts of the body dislodging and traveling to the lungs where it gets stuck in the arteries supplying the lungs. Because the blood clots block the blood going the lungs, PE can be life threatening. Blockage of one of the pulmonary arteries can subsequently lead to sudden onset pleuritic chest pain, decreased oxygen saturation in the blood, passing out and in some cases even death. The purpose of this paper is to provide essential information about the pathophysiology of the disease and to discuss the different treatment modalities that are used in the acute setting for PE.

4. Epidemiology

The term venous thromboembolism (VTE) is a term that includes both DVT and PE. The current evidence states that venous thromboembolism comes right after cardiac ischemic syndromes and stroke on the list of most common acute cardiovascular diseases. The incidence of VTE is estimated to be approximately 60 to 70 per 100,000 people(1). The actual incidence of patients getting PE is believed to be higher than the numbers already mentioned. This is partly due to the fact the a so called silent PE can occur and it may remain asymptomatic over a longer time, until they eventually die of VTE related issues. If we consider age and take that into the equation, we can expect a larger number of patients being diagnosed with and to die of PE in the future. The population of the world is only getting older and seeing that the risk of developing PE is increasing in patients over 40 years and almost doubles with each subsequent decade, we can expect the incidence of PE to be rising in the future(2). In children, the incidence is approximately half of what it is for adults.

The most severe clinical manifestation of VTE is acute PE. Its important to keep in mind that in most cases, PE is a direct consequence of DVT. Most of the data that exists regarding epidemiology and risk factors PE and DVT have been examined as one condition.

5. Etiologies and Pathogenesis

5.1 DVT

A study done with 100 patients diagnosed with DVT, it was found that its etiology could be defined for in 81% of the patients. In this group of patients, the etiologies were split into two different main groups; plasma defects and non-plasma defects. The plasma defects can be further divided into two subgroups: hereditary or acquired(3).

Non-plasma Defects and Deep Vein Thrombosis

Fifty-five percent (55%) of the patients with definable etiologies had a non-plasma defect as a cause of their DVT. The largest group was due to malignancy and had 11%. The remaining in a descending order: 10% was due to arthroscopy, 8% after major trauma, 7% after orthopedic surgery, 6% were morbidly obese, 3% of the patients were ingesting Premarin (conjugated estrogen product), another 3% had diabetes mellitus, 2% had giant cavernous hemangiomas of a thrombosed extremity and lastly, 1% consisted of hereditary spherocytosis, pregnancy, mitral valve prolapse, chronic immobility and ingestion of oral contraceptives(3).

Plasma Defects and Deep Vein Thrombosis

Plasma defects accounted for forty-seven (47%). These defects include hypercoagulability and thrombosis. As already mentioned, the plasma defects of DVT can be split into hereditary and acquired. Out of these fourty-seven percent, 28% were acquired and 19% were congenital. Out of the twenty-eight percent of the acquired defects, 24% had anticardiolipin deficiency and 4% had a lupus anticoagulant. Of the remaining 19% having congenital defects, 8% of the patients had protein S deficiency, another 8% had antithrombin 3 deficiency, 2% had protein C deficiency and only 1% was found to have congenital tissue plasminogen activator (t-PA)

As we can see from these numbers, the non-plasma (55%) defects were a bit more common than the plasma defects (47%). Out from the non-plasma defects, malignancy, arthroscopy, trauma and orthopedic procedures were responsible for most of the etiological disorders associated with DVT. In the patients having a plasma disorder as their cause of DVT, acquired defects were more common than congenital defects (3).

5.2 PE

There are three primary factors that are predisposing a patient to formation of blood clots. The three factors include 1) endothelial injury, 2) stasis or turbulence of blood flow and 3) hypercoagulability of blood. These three together form what is known as Virchow´s triad. The causes of PE are often multifactorial and it is rarely apparent what exactly the cause is. PE usually occur from a thrombi being lodged from one of the deep veins in the lower extremities. Having that said, it ca also arise from the veins in the pelvic region, renal or upper extremities or the right heart chambers. Although the latter examples are rare, the do occur. The list of possible causes is long and includes the following: venous stasis, hypercoaguable states, immobilization, surgery or trauma, pregnancy, oral contraceptives and estrogen replacement, malignancy and hereditary factors. The location of the thrombus inside the lungs, depend entirely on its size. Larger thrombi have a higher chance of being stuck in the bifurcation of the main pulmonary artery while smaller thrombi often travel more distally in the lungs where they only occlude one of the smaller vessels.

Acute PE affects both gas exchange and the circulation. As already mentioned, there are many different cases of PE and they´re often multifactorial. Right ventricular (RV) failure due to pressure overload is believed to be one of the main causes for death in cases of severe PE.

The arterial pressure in the pulmonary arteries increases only if more than 30-50% of the total area of the pulmonary artery´s lumen is occluded by thromboemboli (4). Another cause of constriction of the pulmonary artery´s lumen in the setting of PE is due to PE-induced vasoconstriction. This is mediated by release of thromboxane A2 and serotonin, which contributes to the initial increase in vascular resistance and thereby the arterial pressure in the pulmonary arteries. This effect can be reversed by vasodilators.

This sudden increase in the vascular resistance in the pulmonary arteries has an effect backwards on the right ventricles causing them to dilate and change their contractile properties of the right ventricular myocardium (frank starling mechanism). The subsequent increase in RV volume and pressure are causing the wall tension and myocyte stretch to increase. These compensatory mechanisms just mentioned together with systemic vasoconstriction cause an increase in arterial pressure in the pulmonary arteries and thus improving the blood flow through the obstructed pulmonary vessels and thereby temporarily stabilizing the systemic blood pressure. The adaptive abilities of the RV is limited due to its thin-walled properties. The right ventricle is, under normal conditions unable to generate a mean arterial pressure in the pulmonary arteries above 40mmHg.

The increased workload of the RV causes the contraction of the RV to be prolonged. This in turn cause the interventricular septum to be bowing inwards to the left ventricle (LV) (5). This desyn-

chronization of the ventricles during the early diastole may result in development of a right bundle branch block. Also, as a secondary effect to the interventricular septum bulging into the LV, it may lead to reduction of cardiac output from the LV and can contribute to systemic hypotension and hemodynamic instability.

Respiratory failure in PE is manly due to hemodynamic disturbances (6). The zones in the lungs with obstructed vessels have reduced blood flow. At the same time, other zones have an overflow of blood in the capillary beds due to the temporarily increased pulmonary pressures, resulting in ventilation-perfusion mismatch which contributes to hypoxia. Its been shown that in one third of patients with PE, a right-to-left shunt take place through a patent foramen ovale (PFO) (7). This shunt is caused by an inverter pressure gradient between the left and right ventricles. This may lead to severe hypoxaemia together with an increased risk of paradoxical embolization and stroke. Even in cases where the hemodynamic stability is unaffected, the small emboli that traveled to the distal part of the lungs may create areas of alveolar hemorrhage. This hemorrhage can have different clinical presentations, for example hemoptysis, pleuritis and pleural effusion. This is known as a pulmonary infarction. The effect of pulmonary infarction is usually milder than that of a more proximal occlusion (except in patients with pre-existing cardiorespiratory disease).

6. Clinical Presentation

PE can be present with very diffuse symptoms and can often escape diagnosis. The symptoms are often non-specific. Although often non-specific, there are clinical signs that still raises the suspicion of PE. This includes dyspnoea, chest pain, pre-syncope/syncope, and/or haemoptysis. Rare, but severe presentations include hypotension and shock. These two latter presentations can indicate a more central PE or a severely reduced haemodynamic reserve. As seen in figure 1, syncope is a rare presentation, but it may occur with or without the presence of haemodynamic instability (8). PE can also be completely asymptomatic and can be an accidental discovery during a work-up for another disease or during an autopsy.

Chest pain is a common symptom of PE and is caused by irritation of the pleura due to distal emboli that are causing pulmonary infarct. If the emboli is placed more central, the chest pain is often more of an angina character. The most common presentation, dyspnea, may be acute and severe in more central PE while in the smaller distal ones, it may be mild and transient.

Feature	PE confirmed (*n* = 1880)	PE not confirmed (*n* = 528)
Dyspnoea	50%	51%
Pleuritic chest pain	39%	28%
Cough	23%	23%
Substernal chest pain	15%	17%
Fever	10%	10%
Haemoptysis	8%	4%
Syncope	6%	6%
Unilateral leg pain	6%	5%
Signs of DVT (unilateral extremity swelling)	24%	18%

Figure 1: Clinical signs for PE.
Adapted from European Society of Cardiology (ESC) 2014 guidelines on the diagnosis and management of acute pulmonary embolism. (8)

7. Initial Assessment

The initial assessment of patients suspected to have PE includes medical history taking, an assessment of vital signs, physical exams (including lower extremities to rule out DVT as a potential cause) and blood work. Well´s criteria for pulmonary embolism is a scoring system developed to be able to assess how likely it is for a patient to possibly have PE (9).

-2-0p → Low probability

1-2p → Moderate probability

3-8p → High probability

Wells criteria for the prediction of deep vein thrombosis (DVT)[a]

Clinical Characteristic	Score
Active cancer (patient either receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)	1
Paralysis, paresis, or recent cast immobilization of the lower extremities	1
Recently bedridden for ≥ 3 days, or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swelling	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (non-varicose)	1
Previously documented deep vein thrombosis	1
Alternative diagnosis at least as likely as deep vein thrombosis	-2

[a] Wells scoring system for DVT: -2 to 0: low probability, 1 to 2 points: Moderate probability, 3 to 8 points: high probability

Figure 2: Wells criteria
Adapted from Wells criteria for DVT is a reliable clinical tool to assess the risk of deep venous thrombosis in trauma patients by Greg J. Beilman (9).

8. Laboratory Studies And Diagnostic Procedures

8.1 D-dimer Testing

D-dimers is a test widely used in many different diagnoses. It is ordered through a normal blood test. D-dimers are frequently elevated in patients with cancer, in hospitalized patients and during pregnancy. They are elevated in the plasma in during the process of acute thrombosis due to activation of coagulation and fibrinolysis. Since D-dimers can be elevated in any condition having clot formation and breakdown, it is not a test that is specific for making the diagnosis of either DVT or PE. Meaning the positive predictive value of D-dimers in confirming DVT or PE is very low. On the other hand, the negative predictive value of D-dimer testing is very high, meaning that a negative D-dimer deems the diagnosis of acute DVT or PE to be unlikely.

The specificity of using D-dimers as a tool to rule out PE is steadily decreasing as the age increases. In a patient with more than 80 years of age, the specificity is down to only 10%. Some recent evidence suggest that using different cut-off values for different age groups to improve the performance of D-dimer testing in the elderly (2,10). A recent meta-analysis concerning age-adjusted cut-off values (age x 10µg/L above 50 years) improved the specificity from 34 to 46% while keeping the same sensitivity above 97%.

8.2 Computed Tomographic Pulmonary Angiography

Computed Tomographic (CT) angiography has become the method of choice in order to image the pulmonary vasculature in patients that are expected to have PE. CT angiography allows proper visualization of the pulmonary vessels down to the segmental level. In patients with a low to intermediate clinical suspicion of PE assessed by the Wells criteria as mentioned above, a negative CT scan had a high negative predictive value for PE.

In a study done on the effectiveness of managing suspected pulmonary embolism combining clinical probability, D-dimer testing and CT angiography; all patients were classified as likely to have PE by the Wells criteria or those who had a positive D-dimer test underwent a chest multiple detector computed tomography (MDCT) scan. In these patients, it was shown that the three month thromboembolic risk in the patients that were left untreated because of a negative CT scan was very low (only 1,1%), proving the good negative predictive value of a CT scan in low to intermediate probability (11). Two other randomized control trials reached the same conclusion. A trial done in Canada, comparing a ventilation-perfusion (V/Q) scan and a CT scan, proved that only 7 out of the

531 patients (1,3%) with a negative CT scan had a DVT, while one patient had a thromboembolic event during a later control (12). These results prove that the three to four moth thromboembolic risk would have been only 1,5% if only a CT scan had been performed.

When these data are considered together, they suggest that a negative MDCT is an adequate criterion fro excluding PE in all patients except those with a high clinical probability. It is still considered to be controversial whether patients with a high clinical probability and a negative CT scan should be further investigated. Also, it should be taken into consideration that the positive predictive value of a MDCT scan is lower in patients with low clinical probability for PE. In these patients, further investigation should be considered.

8.3 Lung Scintigraphy

Ventilation-perfusion scintigraphy (V/Q scan) is a diagnostic test that can be performed when PE is suspected. The test is performed with intravenous injection of the radioactive substance technethium (Tc) 99m-labeled macroaggregated albumin particles. These small particles block a small portion of the capillary bed in the lungs, which allows for assessment of lung perfusion. This perfusion scan is combined with ventilation scans using tracers such as for example xenon-133 gas. The usage of the ventilation scan is to increase specificity. The ventilation is expected to be normal in hypoperfused segments in the setting of acute PE. The radiation exposure. In a V/Q scan around 1,1mSv for an adult, which is significantly lower than the radiation exposure from a CT scan (2-6mSv) (6). Taking this into consideration, and the fact that there is no contrast usage in a V/Q scan, it can be applied to patients with a low clinical probability, in young patients, pregnant, in patients with a history of reaction to contrast medium or in patients with severe renal failure.

8.3 Pulmonary Angiography

Pulmonary angiography was for decades the “gold standard” tool to diagnose or to exclude PE. Today, the pulmonary angiography has largely been replaced by the less-invasive CT angiography because of its similar diagnostic accuracy and the fact that it is less invasive. Pulmonary angiography is today used more used to guide percutaneous catheter-directed treatment of acute PE. The visualization of PE using pulmonary angiography is the evidence of a thrombus, either as a filling defect of the contrast or as amputation of a pulmonary arterial branch. These are considered to be direct signs of PE, but there are also indirect signs. Indirect signs include slow flow of contrast, regional

hypoperfisuon, delayed or decreased pulmonary venous flow. These however are not validated signs of PE and can therefore not be considered to be diagnostic.

Every invasive procedure carries a risk and pulmonary angiography is no different. A study done on 1111 patients showed that procedure-related mortality was at 0,5% major non-fatal complications happened in 1% of cases and minor complications in 5% of patients (13). Most of the deaths occurred in patients that were hemodynamically unstable or had respiratory failure.

8.4 Diagnostic strategies

The prevalence of patients actually having confirmed PE that are undergoing diagnostic work-up due to clinical suspicion is low (10-35%) (11). Therefore, use of a diagnostic algorithm is useful. Various combinations of plasma D-dimers and imaging tests have been validated. These algorithms were tested in the emergency room, during the hospital stay or in a primary care setting in patients that were believed to have PE. The failure to follow these evidence based diagnostic strategies and not administering anticoagulation was associated with an increase in the number of VTE and sudden death during the three-month follow-up. The simplest and most straight forward algorithm for suspected PE is to differentiate between patients with or without shock or hypotension – as presented in figures 3 and 4 (8).

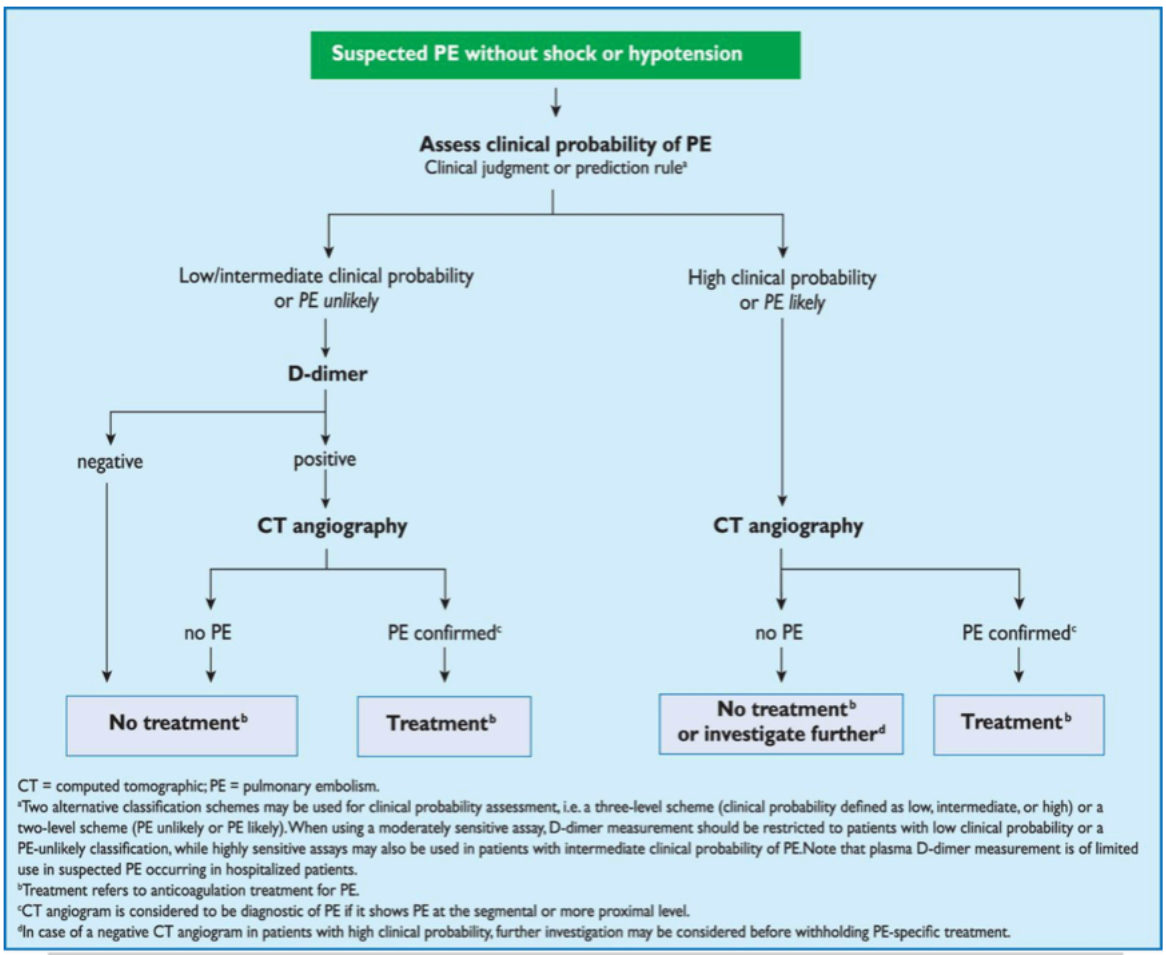

Figure 3: Algorithm for PE without shock or hypotension. Adapted from European Society of Cardiology (ESC) 2014 guidelines on the diagnosis and management of acute pulmonary embolism (8).

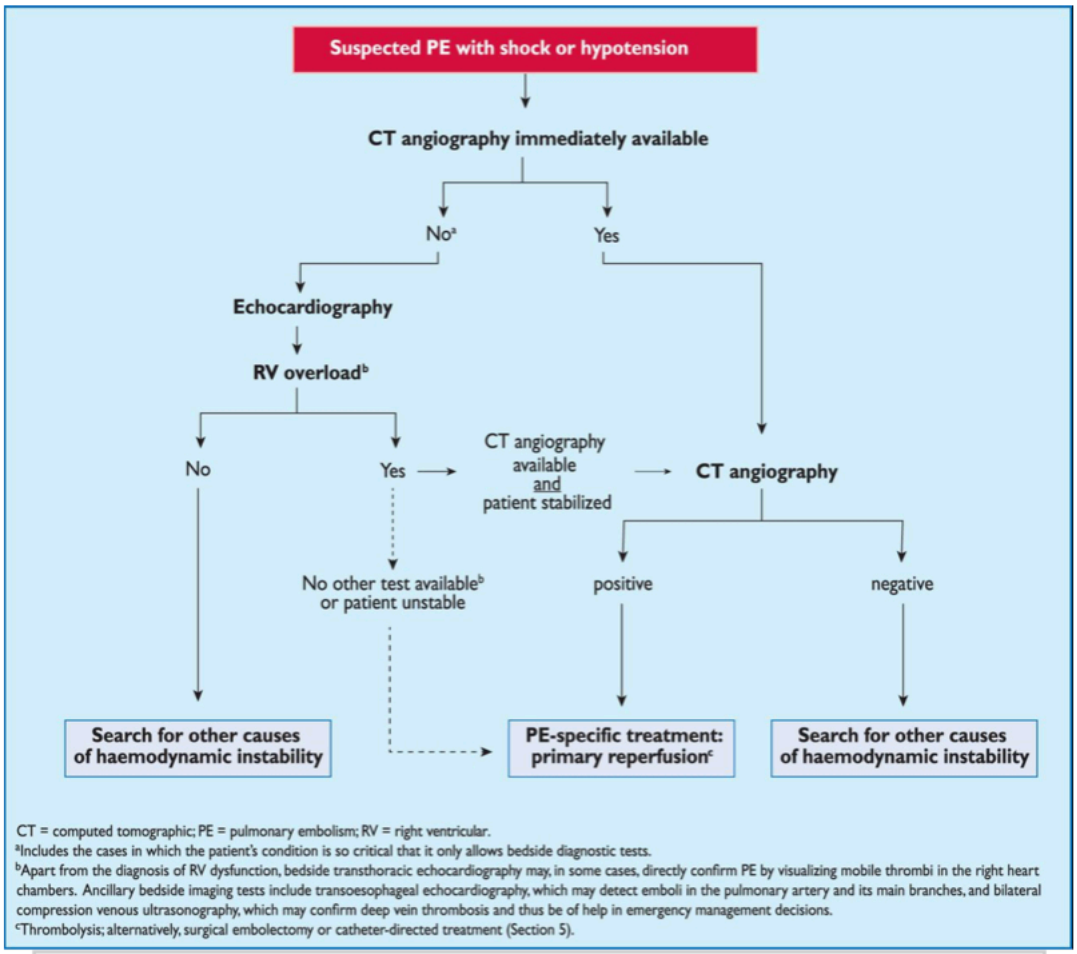

Figure 4: Algorithm for PE with shock or hypotension. Adapted from European Society of Cardiology (ESC) 2014 guidelines on the diagnosis and management of acute pulmonary embolism (8).

9. Management in the Acute Setting

9.1 Hemodynamic and Respiratory Support

The leading cause of death in patients with high-risk PE is acute RV failure that is resulting in low systemic output. Supportive treatment is crucial in patients with PE and RV failure. A study done, show that aggressive volume expansion proves no benefit in these conditions and may even worsen the RV function due to mechanical overstretch. Its been shown that moderate fluid resuscitation (around 500ml) may help to increase cardiac index in patients with PE (14). The usage on norepinephrine as a vasopressor appears to improve the RV function through a direct inotropic effect, and at the same time also improving the coronary perfusion by peripheral alpha-receptor stimulation.

Usage of vasodilators in the setting of PE decrease the pulmonary arterial pressure and the vascular resistance in the pulmonary arteries. The only problem with this treatment modality is that the vasodilators lack specificity for the pulmonary vasculature after intravenous injection.

9.2 Anticoagulation Therapy

Anticoagulation is always recommended in patients with acute PE. This is to prevent early death and recurrent symptomatic or fatal VTE. Acute phase treatment consist of parenteral anticoagulation; unfractionated heparin (UFH) or low molecular weight heparin (LMWH) for 5-10 days. This parenteral heparin should eventually start to overlap with vitamin K antagonist (VKA), or it can be followed up with administration of one of the newer anticoagulants (dabigatran or edoxaban). The normal duration of anticoagulant treatment should be over 3 months.

9.3 Parenteral Anticoagulation Therapy

Patients that have high or intermediate clinical probability for PE, should start parenteral anticoagulation while awaiting the results of the diagnostic testing. Immediate anticoagulation can be granted through use of parenteral anticoagulants, such as intravenous UFH, subcutaneous LMWH or subcutaneous fondaparinux. LMWH and fondaparinux are usually preferred rather than UFH for initial anticoagulation due to lower risk of major bleeding and inducing heparin induced thrombocytopenia (HIT). UFH is recommended for those patients with serious renal impairment (creatinine clearance < 30mL/min) or severe obesity.

Fondaparinux is a factor Xa inhibitor. It is administered once daily through subcutaneous injections without the need for monitoring.

9.4 Vitamin K Antagonists

Oral anticoagulants should be administered as soon as possible. VKA has been the “gold standard on oral anticoagulants for decades (15). Because of its long time to reach it´s actual therapeutic window, anticoagulation with UFH, LMWH or fondaparinux should start before these oral anticoagulants and they should be continued for at least 5 days until the international normalized ration (INR) has reached between 2,0 – 3,0 for two consecutive days.

9.5 Novel Oral Anticoagulant (NOAC) Therapy

This group of drugs was introduced to the marked in the US in 2010 (16). Initially this group of drugs were known as “non-vitamin K oral antagonist oral anticoagulants” but eventually changed name to “novel oral anticoagulants”. Today the most popular term for the group is direct oral anticoagulant (DOAC). The latter reflects the mechanism of these types of anticoagulants. Instead of reducing production of clotting factors (like warfarin) or binding to antithrombin 3 in order to induce anticoagulation (like heparin), these newer drugs (like dabigatran) binds directly to clotting factor 2a. A study done in patients with VTE compared the newer drug Edoxaban (factor Xa inhibitor) with conventional therapy with warfarin in 8240 patients. It proved that the patients that received Edoxaban had non-inferior results after a 12 month follow-up (17).

9.6 Thrombolytic Treatment

Thrombolytic treatment of acute PE restores perfusion more rapidly than anticoagulation with UFH alone (18). This early resolution of the obstruction in the pulmonary vessels leads to reduction in pulmonary artery pressure and secondarily an improvement in RV function. These hemodynamic benefits of thrombolytic treatment are confined to the first few days only. In patients that survives, the differences between anticoagulant therapy versus thrombolytic treatment, there is no clear difference between the two after one week.

9.7 Surgical Embolectomy

Surgical embolectomy is the physical removal of the obstruction. It is indicated in a few patients; high-risk patients, especially thrombolysis is contraindicated or has failed. The procedure itself of removing the actual obstruction is not a very technical one.

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11. Biography

I was born in Oslo, Norway on May the 15th 1990. I grew up in a place in the outskirts of Oslo called Nesodden where I completed primary school and high school).
In my spare time outside of school, I trained and competed in cycling, running and cross country skiing. Doing this through my youth made me develop a love for training, which has made me always continue with some form of exercising.

Right after completing high school I enrolled to the army in the storm engineer platoon and moved to the northern Norway for a year. After ended service, I returned to my hometown where I worked in a kindergarten for almost 3 years. As a developed a growing interest for the field of medicine, I moved to Stockholm, Sweden to complete a pre-medical course where I applied and got accepted to Zagreb medical school.

I studied medicine in Zagreb in the period of 2013 and 2019. I enjoyed the life in medical school and the life on Croatia outside the university. During the breaks we had between semesters, I had different jobs in the medical field. I for example worked in a closed ward in psychiatry and in rehabilitation for patients with traumatic brain injuries. In 2019 I finished medical school in Zagreb and my clinical rotations back in Norway.