CASE REPORT

Treating pulmonary embolism in the intensive care unit: are the guidelines helpful?

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Abstract

Patients admitted to the intensive care unit (ICU) with pulmonary embolism (PE) usually have an increased mortality risk. This risk can be estimated by the Pulmonary Embolism Severity Index (PESI), composed of clinical features such as tachycardia, tachypnoea, hypotension, altered mental status and decreased arterial oxygen saturation. Patients with persistent hypotension (systolic blood pressure <90 mmHg for ≥15 min) carry the highest mortality risk and in the absence of contraindications, international guidelines recommend to treat these patients with fibrinolysis. Choosing the best anticoagulation strategy for patients with acute PE can be difficult, especially in patients with severe obesity and those with contraindications to anticoagulation. Although the guidelines suggest that intermittent subcutaneous and continuous intravenous anticoagulant treatment are equally effective, the intermittent subcutaneous treatment does not warrant continuous protection against clinical deterioration. To illustrate this problem, we present two cases of patients with severe PE admitted to the ICU.

Introduction

Pulmonary embolism (PE) covers a wide spectrum of clinical severities, ranging from low-risk to life-threatening. The severity of PE is classified according to its short-term mortality risk: low (<1%), intermediate (3-15%) and high (>15%).[1] Patients with low-risk PE are characterised by a normal blood pressure, normal biomarkers and no right ventricular dysfunction.[2] Patients with high-risk PE can be identified by clinical features such as tachycardia, tachypnoea, hypotension, altered mental status and decreased arterial oxygen saturation, parameters incorporated in the Pulmonary Embolism Severity Index (PESI) *(table 1)*.[1-3] Patients in circulatory shock carry the highest risk of short-term mortality (>15%). Although this classification is clear-cut, choosing the right anticoagulant strategy for a

particular ICU patient with PE can be difficult. To illustrate this problem, we present two case histories.

Case 1

A 49-year-old woman with a body mass index (BMI) of 43.5 kg/m² (height 176 cm, weight 135 kg) was admitted to the hospital because of chest pain and dyspnoea. Her body temperature was 37.1°C, heart rate 143/min, blood pressure 118/71 mmHg and respiratory rate 18/min. Based on age and heart rate, a PESI score of 69 could be calculated (class II) *(table 1)*. CT angiography demonstrated large emboli in the left and right pulmonary arteries *(figure 1)*. Laboratory results showed a

Table 1. PESI score

Parameter	Points
Age	Age in years
Male gender	+ 10
Cancer	+ 30
Chronic heart failure	+ 10
Chronic pulmonary disease	+ 10
Heart rate >110/min	+ 20
Systolic blood pressure <100	+ 30
Respiratory rate >30/min	+ 20
Temperature <36°C	+ 20
Altered mental status	+ 60
SaO2 <90%	+ 20

Class I:	≤65 points: very low 30-day mortality risk (0-1.6%)
Class II:	66-85 points: low mortality risk (1.7-3.5%)
Class III:	86-105 points: moderate mortality risk (3.2-7.1%)
Class IV:	106-125 points: high mortality risk (4.0-11.4%)
Class V:	>125 points: very high mortality risk (10-25%)

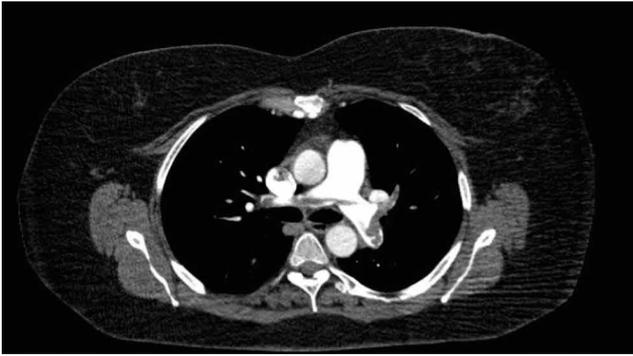PESI = Pulmonary Embolism Severity Index; SaO2 = arterial oxygen saturation.

Figure 1. CT scan of patient 1

leukocyte count of 12.8 x 10⁹/l and an hs-troponin-T level of 0.073 μg/l. The patient was treated with 5000 IU unfractionated heparin (UFH) intravenously, followed by nadroparin 9500 IU subcutaneously twice daily on the first day of admission and 7600 IU thrice daily the day after. On the third day of admission the patient experienced renewed chest pain along with dyspnoea, nausea and dizziness. Monitoring showed a temperature of 38.1°C, heart rate of 117/min, blood pressure of 98/69 mmHg, respiratory rate of 20/min and peripheral oxygen saturation of 95%. There were no clinical signs of infection and the anti-Xa activity was 0.01 U/ml. The patient was admitted to the ICU, treated with UFH intravenously and the symptoms subsided. Three days later, she could return to the ward and ten days later, she left the hospital.

Case 2

A 63-year-old man with a BMI of 24 (height 195 cm, weight 91 kg) had a right-sided hemicolectomy because of colonic cancer. On the third postoperative day he was admitted to the ICU because of fever, chills and desaturation. He had a body temperature of 38.5°C, heart rate of 117/min, blood pressure of 134/95 mmHg, respiratory rate of 20/min and peripheral oxygen saturation of 90%. Based on age, male gender, cancer and heart rate, a PESI score of 123 could be calculated (class IV) *(table 1)*. The next day, CT angiography showed large emboli in the arteries of the lower right lobe and both left lobes. The patient was treated with subcutaneous nadroparin, 5700 IU twice daily. A week after the operation, the nadroparin dose was increased to 7600 IU twice daily, acenocoumarol was added and the patient was transferred to the ward.

Two days later, the patient experienced acute dyspnoea. Monitoring showed a heart rate of 150/min, respiratory rate of 40/min and oxygen saturation of 88%. Oxygen was applied through a non-rebreather mask and the patient was admitted to the ICU. Because massive PE was suspected, the patient was treated with 5000 IU UFH and 100 mg recombinant tissue plasminogen activator intravenously. Nevertheless, the heart rate and blood pressure dropped until cardiac arrest with

pulseless electric activity occurred. The resuscitation no-shock block was started according to the guideline of the European Resuscitation Council (ERC). Despite adequate basic life support and repeated administration of epinephrine intravenously, echocardiography showed no cardiac activity, a dilated right ventricle and collapse of the left ventricle, compatible with massive PE. After 40 minutes, the resuscitation was ended and the patient was pronounced dead.

Discussion

In both cases described here, PE was accurately diagnosed. Both patients were admitted to the ICU and treated with anticoagulants. However, the first patient recovered, while the second patient died. This prompted us to investigate whether treatment for PE in the ICU can be optimised.

Patients with suspected PE should be stratified according to their short-term mortality risk.[1] For this purpose, PESI can be used *(table 1)*.[1] PESI has been derived and validated in patients with PE admitted to the hospital.[3,4] When calculated for our patients, the first patient had a PESI score of 69 points (class II), corresponding to a low mortality risk (1.7-3.5%), whereas the second patient had a PESI score of 123 (class IV), corresponding to a high mortality risk (4-11.4%).[1] When interpreting these scores, we have to keep in mind that in PESI classes I-IV, the score has a negative predictive value ranging from 76 to 92%, whereas the positive predictive value ranges from 27 to 50%.[5]

Several investigators have tried to improve the predictive value of PESI by adding biomarkers or information derived from imaging. By adding troponin, BNP or leukocyte count to the PESI score, its predictive value could be improved.[6-8] In addition, cardiac chamber sizes measured during CT angiography were demonstrated to have a predictive value for outcome: a left atrial volume ≤62 ml, a left ventricular volume ≤67 ml and a right to left atrial ratio >2.1 were associated with hazard ratios for 30-day mortality ranging from 1.8 to 2.4.[9] A right atrium to ventricle ratio <1.01 was predictive of 30-day mortality.[10] Right ventricular strain, defined as a right to left ventricle ratio ≥1, was identified as a predictor of negative outcome with an odds ratio of 9.2.[11]

The American Heart Association (AHA), the European Society of Cardiologists (ESC) and the American College of Chest Physicians (ACCP) have all published guidelines for the management of pulmonary embolism.[2,12,13] All three guidelines recognise the impact of right ventricular dysfunction and elevated cardiac markers such as troponin and natriuretic peptide on short-term mortality. However, the routine determination of these items is not recommended because of their low positive predictive value.[12]

Patients with established PE should receive prompt and appropriate anticoagulation. Anticoagulant strategies comprise

intravenous UFH and subcutaneous fondaparinux, low-molecular-weight heparin (LMWH) or UFH. The three guidelines recommend fibrinolysis for patients with acute PE associated with shock (defined as a condition of inadequate tissue perfusion) or hypotension (defined by the ESC guideline as a blood pressure <90 mmHg for ≥15 minutes or a systolic pressure drop by ≥40 mmHg for ≥15 minutes, if not caused by new-onset arrhythmia, hypovolaemia or sepsis) and no contraindications. In these patients, the ESC guideline recommends anticoagulation with UFH because of its short half-life, the ease of monitoring its anticoagulant effects, and its rapid reversal by protamine.[12] Patients with acute PE without hypotension should be stratified by means of PESI and markers of right ventricular strain to determine their eligibility for fibrinolysis.[12,13] In patients with a high mortality risk, the AHA guideline suggests heparin anticoagulation, while the ACCP guideline suggests 'aggressive anticoagulation' without further specification.[2,13] The ESC guideline recommends UFH for patients in whom primary reperfusion such as thrombolysis or embolectomy is considered, as well as for those with serious renal impairment (creatinine clearance <30 ml/min) or severe obesity (BMI >35 kg/m^2).[12] In patients with renal impairment, decreased heparin clearance may lead to heparin-associated bleeding. Therefore, UFH by continuous infusion has to be monitored by means of the activated partial thromboplastin time (APTT) or the activated clotting time.[14] Several authors have described the possibility to estimate the risk of bleeding in patients with venous thromboembolism. Kooiman et al. demonstrated that patients with a HAS-BLED score >3 had an increased risk of bleeding.[15] Among acutely ill medical patients, Guijarro et al. demonstrated an increased risk of bleeding in males, patients with ischaemic heart disease, upper gastrointestinal disease, liver disease, coagulation disorders and anemia, with odds ratios ranging from 1.09 to 3.01.[16] In patients with morbid obesity (BMI >40 kg/m^2), the effect of subcutaneously administered LMWH is delayed, and is best described by a three compartment model.[17] If there is a compelling reason to choose LMWH in a patient with morbid obesity, anti-Xa monitoring is recommended, aiming at an anti-Xa level of 1.3 IU/ml four hours after the subcutaneous dose.[14,18] For patients with cancer-associated PE, the three guidelines recommend LMWH as the therapy of choice.[2,12,13]

When we reconsider the treatment of our patients, the first patient had a BMI of 43.5 and a low mortality risk (1.7-3.5%) based on a PESI score of 69 (class II). According to the ESC guideline, she should have been treated with UFH, preferably a bolus of 60 IU/kg, followed by a continuous infusion of 12 IU/kg/h.[19] If there is a compelling reason to choose for LMWH, the recommended daily subcutaneous nadroparin dose is 171 IU/kg, aiming at an anti-Xa level of 1.3 IU/ml four hours after the subcutaneous dose.[12,18] It should be noted that

intermittent subcutaneous dosing of LMWH leads to anti-Xa trough and peak levels between 0 and 1.7 IU/ml, whereas an anti-Xa level of 1.0±0.2 IU/ml is needed for an adequate anticoagulant effect.[18,20] The anti-Xa level in our patient was 0.01 IU/ml 5 hours after the subcutaneously administered nadroparin.

Our second patient underwent surgery for colonic cancer and according to the three guidelines, LMWH was the treatment of choice.[2,12,13] This patient had a PESI score of 123 (class IV) and therefore a high mortality risk (4-11.4%). For high-risk patients, the AHA guideline recommends aggressive anticoagulation without further specification. When nadroparin is chosen as first-line therapy, the recommended daily dose is 171 IU/kg, which comes down to 15,561 IU per day for our patient. The prescribed subcutaneous dose of 5700 IU nadroparin twice daily was therefore too low. In patients with cancer, aggressive anticoagulation is important, since both cancer and failure to rapidly achieve therapeutic levels of anticoagulation independently predict an increased risk of recurrence.[12,21-23] In a large case-cohort study, Heit et al. found a hazard ratio of 3.5 (95% CI 1.86-6.66) for recurrence of thromboembolism among patients with stage 4 cancer, and a hazard ratio of 1.6 (95% CI 1.12-2.39) for patients failing to reach a therapeutic APTT within 24 hours.[21] In an earlier study, Heit et al. found a hazard ratio of 0.57 (95% CI 0.34-0.97) for recurrence of thromboembolism among patients reaching an APTT ≥58 s. within 24±4 hours, which corresponded to an anti-Xa level of ≥0.3 IU/ml.[23] For treatment with LMWH, however, routine anti-Xa monitoring is not recommended. Moreover, the correlation between anti-Xa level and antithrombotic activity is weak.[20,24] The question remains how we can be sure that the chosen anticoagulant strategy adequately protects our patients from recurrent thromboembolism. When we choose UFH by continuous infusion, the risk of recurrent thromboembolism decreases by 43% when an APTT ≥58 s. is reached, whereas we cannot be sure about the risk of recurrence when intermittent subcutaneous LMWH is used.

Reconsidering the three international guidelines for the management of PE, subtle differences in the recommendations for the treatment of severely obese patients and high-risk patients are noticed. Obviously, these guidelines are based on large populations of patients who were not necessarily critically ill. When treating our critically ill PE patients, we should realise that in general, they have a higher mortality risk than the average PE patient included in a treatment trial and that, therefore, our patients have to be treated more aggressively. When choosing an anticoagulant for our critically ill PE patient, we should take into account body mass index, disease severity and risk of recurrence, both for the individual patient and the anticoagulant strategy chosen.

Conclusion

Critically ill patients with pulmonary embolism usually have a higher mortality risk than the average patient included in a treatment trial. Therefore, guidelines for the treatment of pulmonary embolism are often not aggressive enough for our high-risk ICU patients. When we treat ICU patients with acute PE, we have to take into account the BMI, disease severity and risk of thromboembolic recurrence. For the estimation of disease severity, PESI may be helpful. In both severely obese and high-risk ICU patients with pulmonary embolism (PESI classes IV and V), we should choose an anticoagulant strategy minimising the risk of thromboembolic recurrence, such as UFH by continuous infusion, reaching an APTT ≥58 s. within 24 hours.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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