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Challenges and considerations in the management of acute pulmonary embolism: a critical analysis of European Society of Cardiology guidelines

Izazovi i razmatranja u lečenju akutne plućne embolije: kritička analiza smernica Evropskog društva kardiologa

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Introduction

In 2019, the European Society of Cardiology (ESC) published guidelines for the management of acute pulmonary embolism (PE), with no revisions planned until 2026 [1]. This absence of updates is primarily due to the lack of significant randomized trials influencing current clinical practices. Nevertheless, this raises concerns, as the 2019 ESC PE guideline leaves substantial gaps in addressing critical clinical scenarios. This article aims to evaluate these unaddressed issues, focusing on the challenges faced in the everyday management of patients with acute PE.

Patients with pulmonary embolism in resuscitation

The mortality rate among patients experiencing acute PE and requiring resuscitation is inadequately addressed in current guidelines. Three possible scenarios necessitate consideration. First, in cases where it is unknown whether a patient admitted in a state of reanimation has acute PE, physicians must swiftly estimate the probability that cardiac arrest (CA) is due to this condition. Crucial information, such as recent surgery, trauma, immobilization, malignant disease, and previous venous thromboembolism (VTE), is imperative. A swollen leg may serve as a potential clue. Information from bystanders is also significant, and if acute dyspnea or severe cyanosis precedes unconsciousness, the likelihood of acute PE increases. The second scenario involves a patient known to have acute PE whose condition suddenly deteriorates. In such cases, it is highly likely that acute PE is the cause of CA. The third scenario presents an acute PE patient in CA with an absolute contraindication for thrombolysis.

In each instance, prompt resuscitation measures are warranted, utilizing urgent transthoracic echocardiography (TTE). TTE is critical for the differential diagnosis of CA of unknown cause. The most common causes that should be rapidly differentiated by TTE include cardiac tamponade, dilated cardiomyopathy, or myocardial infarction. In cases where acute PE causes CA, an enlarged and dysfunctional right ventricle is expected to be the dominant finding on TTE [2].

If acute PE is suspected, a bolus of unfractionated heparin, usually 5,000 units, must be administered immediately. If a strong suspicion exists that acute PE is the cause of CA, and there are no obvious absolute contraindications for thrombolytic therapy, a 50 mg tissue plasminogen activator i.v. bolus should be administered [3–7].

If clear contraindications for thrombolysis are present, the only treatment option is catheter-directed therapy (CDT), involving aspiration with or without thrombus fragmentation, or surgical embolectomy [8–10]. However, these options are rarely available.

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Patients with high-risk pulmonary embolism and significant contraindications for thrombolysis

Absolute contraindications for thrombolysis become relative in the presence of life-threatening high-risk PE, given that the mortality rate among high-risk PE patients exceeds 50%. However, certain contraindications pose a substantial hazard for classic systemic thrombolytic therapy. Recent major surgery, intracranial hemorrhage, aortic dissection, or major trauma present almost insurmountable challenges for systemic thrombolysis. Recent years have seen the development of new and highly efficient catheters for thrombus aspiration and fragmentation, such as the FlowTriever® and "Penumbra" systems®, which have undergone relatively large cohort studies demonstrating good efficacy and safety results [8–12]. Despite this, these systems have not been tested according to ESC guidelines recommendations in high-risk PE patients with contraindications for systemic thrombolysis, failed thrombolysis, or in intermediate-high-risk PE patients who deteriorate. Additionally, no randomized trials compare systemic thrombolysis or anticoagulant therapy with these CDTs. The suitability of low-dose catheter-directed thrombolysis in patients at very high risk for bleeding on systemic thrombolytic therapy remains unknown. Local thrombolysis may have an advantage over mechanical devices for lysing distal thrombi and those unreachable with large aspiration catheters. However, local thrombolysis is likely slower in achieving the reperfusion of occluded arteries than mechanical devices. The probable significant obstacle for CDT is the need for relatively large randomized studies to achieve the necessary hard endpoint, which is all-cause mortality for each catheter system in use. Probably more than 500 patients for the experimental and control groups are needed for intermediate-high-risk PE, or at least 100 *per* group for high-risk PE patients.

When to use reperfusion therapy in patients with intermediate-high risk pulmonary embolism

Approximately 10–15% of patients initially presenting with intermediate-high-risk PE experience deterioration in the next few days, evolving into features indicative of high-risk PE. Physicians handling acute PE often choose not to wait for clinical improvement after sole anticoagulation therapy due to concerns about hemodynamic collapse. Many experts advocate for the early initiation of reperfusion therapy to forestall hemodynamic deterioration. Recognizing this critical juncture involves considering small and simple factors, including an increase in heart rate, a decrease in oxygen saturation, an elevation in breathing rate, a slight decrease in arterial blood pressure, or specific laboratory markers (elevated troponin, leukocytosis, increased lactate in arterial blood samples) [13–16]. All these factors carry significance in intermediate-high-risk PE with substantial right ventricle dysfunction (tricuspid annular plane systolic excursion – TAPSE, less than 1.5 cm) and significantly elevated B-type natriuretic peptide – BNP or cardiac troponin blood levels. Should any of these parameters worsen during the initial hours of the treatment, the decision for reperfusion should be promptly made. The assessment of bleeding risk, such as using the Pulmonary Embolism Bleeding Score Index – PEBSI, could aid in determining the appropriate reperfusion therapy [17].

The organization of pulmonary embolism management

In the last decade, the role of Pulmonary Embolism Response Teams – PERT has gained recognition for treating complex patients with acute PE, necessitating a multidisciplinary approach [18]. However, the organization of a PE network is equally essential, as not all hospitals possess the facilities to manage all types of complex PE cases. Some hospitals may emerge as leaders in this field by mastering catheter-guided therapy and surgical thrombectomy as the exclusive options for treating certain PE patients. To achieve this, a robust local infrastructure comprising specialized centers strategically located in specific geographic areas must be operational around the clock. Ensuring effective communication between local health centers, ambulances, and specialized hospitals is pivotal for determining the optimal treatment approach for patients grappling with the intricacies of acute PE.

The timing and choice of anticoagulant therapy

For high-risk PE patients, accurate estimation of renal function is crucial, with unfractionated heparin emerging as the safest therapy from that perspective. If rapid improvement is evident, low-molecular-weight heparins could also serve as the initial choice. In cases of "unclear" patients, considering risk estimation or other diagnostic challenges, low-molecular-weight heparins are recommended if renal clearance exceeds 30 mL/min. Hemodynamically stabilized patients can promptly receive direct oral anticoagulants. Among them, rivaroxaban, with the highest loading dose, may be most suitable for younger patients with a low bleeding risk, while apixaban could present an advantage for older patients and those with higher bleeding risk. Edoxaban has demonstrated favorable outcomes in intermediate-high-risk patients, and the lower dose is permitted and tested in acute VTE based on renal clearance. Dabigatran stands as a viable option when short-term anticoagulation is necessary, such as after major surgery or trauma, given that the lower dose of this drug is not validated for prolonged anticoagulation [19–24]. Following thrombolysis, a delay of at least 1–2 days is advisable before introducing direct oral anticoagulants to ensure patient stabilization. In contemporary practice, the trend is towards shorter hospitalization durations for the treatment of acute PE, even in severe cases, emphasizing the early use of direct oral anticoagulants.

How to manage long-term anticoagulant therapy in patients who had acute pulmonary embolism

The risk of recurrent PE generally diminishes over time for the majority of patients, with two notable exceptions being active-progressive malignant disease and triple-positive anti-phospholipid syndrome. After major surgery or trauma,

the recurrence rate is low in VTE. However, in all other cases, an increased risk of recurrent thromboembolic events exists, presenting similarly to the initial occurrence. Consequently, the majority of patients typically require long-term anticoagulation therapy following the first PE. If the therapy is discontinued 3–6 months after the index event, the recurrent risk is approximately 5–7% *per* year and up to 10% in the first year [25, 26]. Notably, patients with severe PE face a higher risk of mortality with recurrent events, prompting a more liberal approach to the decision for prolonged anticoagulation. This includes patients with some degree of present bleeding risk. Conversely, patients with low-risk PE may not necessitate long-term anticoagulation if they have a high bleeding risk. The authors' stance in this article is that younger patients lacking thrombotic risk factors (such as severe obesity or chronic disease) after a minor transient or persistent risk factor for PE (like minor surgery or trauma, pregnancy, postpartum, long journeys, the use of prothrombotic drugs, or the presence of mild thrombophilia) may not require anticoagulant therapy after 12 months of treatment. However, spontaneous PE and PE related to chronic diseases likely warrant long-term anticoagulation, extending for years. In each case, patients with a higher bleeding risk (where the VTE-BLEED score may assist in risk estimation) should receive a lower dose of direct oral anticoagulants after 3–6 months from the index event or even consider discontinuation of therapy in specific cases [27].

Conclusion

In conclusion, this critical analysis reveals the existing challenges and unaddressed issues in the European Society of Cardiology guidelines for acute pulmonary embolism. Swift evaluation, differentiation through urgent transthoracic echocardiography, and careful consideration of treatment options are pivotal. The need for ongoing research, comprehensive testing of emerging therapies, and a multidisciplinary approach is underscored to enhance acute pulmonary embolism management. This evolving landscape urges clinicians to integrate emerging evidence with established guidelines for optimal patient outcomes.

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Conflict of interest

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