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MANAGEMENT OF ACUTE PULMONARY EMBOLISM: CLINICAL CHALLENGES AND THERAPEUTIC STRATEGIES

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Abstract: Acute pulmonary embolism (PE) is one of the main cardiovascular emergencies, representing the third leading cause of death from vascular causes worldwide. Despite diagnostic advances, early recognition and appropriate management of PE still pose significant challenges to clinical practice, especially in cases classified as intermediate risk, where the therapeutic decision must be individualized and based on multiple parameters. This article carries out a narrative review of the literature, bringing together the most up-to-date evidence on the diagnosis, risk stratification and treatment of PE, with an emphasis on controversial aspects of management and strategies aimed at reducing morbidity and mortality. It highlights the central role of assessing right ventricular function, the careful use of biomarkers, the positive impact of multidisciplinary teams (PERT) and therapeutic innovations such as low-dose thrombolysis and catheter-directed interventions. The importance of longitudinal monitoring to prevent chronic complications, such as thromboembolic pulmonary hypertension, is also highlighted. Given the high prevalence and complexity of PE, technical mastery combined with an integrated, evidence-based approach is fundamental to optimizing clinical outcomes.

INTRODUCTION

Acute pulmonary embolism (PE) represents a highly complex and relevant clinical condition in medical practice, and is currently recognized as the **third most common cause of cardiovascular death in the world**, surpassed only by acute myocardial infarction and stroke. (Kulka et al., 2021), 2021) It is a manifestation of the venous thromboembolism (VTE) spectrum, the pathophysiology of which involves partial or complete occlusion of the pulmonary circulation by emboli, usually originating from deep vein thrombosis of the lower limbs, culminating in consequences ranging from nonspecific and discre-

et symptoms to hemodynamic collapse with imminent risk of death. (Khandait et al., 2023; Kulka et al., 2021)

Despite advances in diagnostic and therapeutic techniques, PE remains a challenge for clinicians, intensivists, cardiologists and emergency physicians. It is estimated that the **annual incidence ranges from 39 to 115 cases per 100,000 inhabitants**, with an increasing prevalence in the elderly - individuals over 80 have up to an eightfold greater chance of developing PE compared to those between 40 and 50 years old. (Kulka et al., 2021) The overall mortality of PE has fallen in recent years, mainly attributed to the introduction of clinical probability scores, the rational use of D-dimer dosage and the improved accuracy of imaging tests, especially pulmonary angiography. (Hobohm; Keller; Konstantinides, 2023) However, around **60% of diagnoses are still made post-mortem**, which highlights the persistent difficulties in identifying the disease early. (Kulka et al., 2021)

Risk stratification in PE is fundamental for therapeutic choice and prognosis. The current classification divides patients into three main groups: low risk, intermediate risk and high risk. Among these, intermediate-risk **PE - also known as submassive PE - is the most challenging subtype to manage**, requiring an individualized approach based on clinical assessment, the presence of right ventricular dysfunction and laboratory markers of myocardial damage. (Machanahalli Balakrishna et al., 2022) Hospital mortality for this group can reach 11.2%, reinforcing the need for precise and up-to-date protocols for its management. (Kulka et al., 2021)

In addition, there has been an increase in the incidence of PE, possibly associated with an ageing population, greater clinical vigilance and the expansion of diagnostic resources. At the same time, the therapeutic approach has evolved significantly, incorporating everything from **conventional anticoagulation to reperfusion strategies** such as systemic thrombolysis, catheter-based interventions and, in selected cases, surgical embolectomy. Assessment of the right ventricle has become an essential component in risk stratification and in defining the initial therapeutic approach (Hobohm; Keller; Konstantinides, 2023).

In this context, intermediate-risk pulmonary embolism (PE) represents a clinical challenge due to its heterogeneity and potential for rapid deterioration, even in the absence of hemodynamic instability. The presence of right ventricular dysfunction and elevated biomarkers such as troponin and BNP is associated with a worse prognosis, requiring a stratified approach that integrates clinical scores, imaging tests and laboratory parameters to guide individualized treatment (Machanahalli Balakrishna et al., 2022; Khandait et al., 2023).

Therefore, given the high prevalence, diversity of clinical presentations and complexity of management, especially in intermediate-risk cases, a critical review of current diagnostic and therapeutic strategies is needed, with an emphasis on the main challenges faced by contemporary clinical practice. This article aims to summarize the main aspects related to the management of acute pulmonary embolism, in the light of the most recent evidence and international guidelines, with the aim of contributing to evidence-based medical conduct and reducing the morbidity and mortality associated with the disease. (Hobohm; Keller; Konstantinides, 2023; Khandait et al., 2023; Kulka et al., 2021; Machanahalli Balakrishna et al., 2022)

METHODOLOGY

This research is a literature review with the aim of compiling and critically discussing the most current evidence on the management of acute pulmonary embolism, focusing on the clinical challenges and therapeutic strategies described in recent scientific literature. The se-

arch for studies was conducted in a structured way in the PubMed database, covering publications from the last five years. To ensure a comprehensive and specific selection, the following combined descriptors were used: "Pulmonary Embolism", "Treatment" and "Diagnosis".

Articles available in their entirety that directly or indirectly addressed the diagnosis and treatment of acute pulmonary embolism were included, as long as they presented thematic relevance, methodological consistency and scientific value. Publications in any language were accepted, including original studies, narrative reviews and update articles. Exclusion criteria included duplicate publications, studies outside the scope of the proposed topic and articles not accessible on the PubMed database.

RESULTS AND DISCUSSION

Advances in diagnostic imaging have revolutionized the assessment of suspected pulmonary embolism (PE) and are at the heart of contemporary PE treatment. Computed tomography pulmonary angiography (CTA) has emerged as the gold standard modality due to its exceptional sensitivity and specificity for visualizing thrombi within the pulmonary artery. Advanced multidetector CT technologies have recently complemented not only the ability to image rapidly with high spatial resolution, but also the ability to measure the size and function of the right ventricle, as expressed in the RV/LV diameter ratio, which is crucial for risk stratification (Baram et al., 2020). At the same time, ventilation/perfusion (V/Q) scintigraphy may still retain a vital role, especially in patients without iodinated contrast for CT, given the prevalence of highly suggestive ventilation-perfusion mismatches (Baram et al., 2020). Point-of-care ultrasound techniques, such as transthoracic focused echocardiography and compressive lower limb ultrasound, have become valuable "up close"

tools for assessing RV size and the presence of concomitant deep vein thrombosis, facilitating rapid therapeutic decisions in critically ill or unstable patients (Baram et al., 2020; Keller et al., 2020). The emerging application of artificial intelligence to image processing is beginning to show potential for fully automated quantification and prognostic assessment of clots, promising greater diagnostic accuracy and reproducibility in the short-term future (Khandait et al., 2023; Leidi et al, 2022).

The therapeutic approach to acute PE is determined by hemodynamic status. In **unstable (high-risk)** patients, careful volume replacement with intravenous fluids is imperative, as excess aggravates right ventricular (RV) dysfunction, while moderate volumes improve cardiac output in the absence of hypervolemia (PANKAJ). Norepinephrine stands out as the preferred vasopressor, with dobutamine as an alternative in cases of low output. (Khandait et al., 2023) Bedside echocardiography confirms RV overload when angiotomography is unfeasible. At the same time, anticoagulation should be immediate, followed by systemic thrombolysis if there are no contraindications, significantly reducing mortality (Kulka et al., 2021).

In **intermediate-high risk** patients, the PEITHO study revealed that thrombolysis with tenecteplase reduces 7-day mortality (2.6% vs. 5.6%), but increases the risk of intracranial hemorrhage (6.3% vs. 1.5%). The implementation of specialized multidisciplinary teams (Pulmonary Embolism Response Teams - PERT) has shown benefits in optimizing the management of pulmonary embolism, especially in intermediate and high risk cases. These teams promote a staggered, personalized and evidence-based approach, integrating specialists in cardiology, pulmonology, interventional radiology and intensive care, which contributes to faster and more effective decisions, as well as better coordination of care (Khandait et al., 2023). The high risk

of intracranial hemorrhage following the use of tenecteplase justifies the preference for initial parenteral anticoagulation (low molecular weight heparin or fondaparinux), with rescue thrombolysis reserved for hemodynamic deterioration. (Hobohm; Keller; Konstantinides, 2023; Khandait et al, 2023) Strategies such as reduced doses of thrombolytics (e.g. urokinase) have shown comparable efficacy to anticoagulation alone, with a similar hemorrhagic safety profile. (Khandait et al., 2023). The benefit of systemic thrombolysis in reducing mortality in patients with intermediate-high risk pulmonary embolism must be weighed against the significant increase in hemorrhagic risk, especially intracranial hemorrhage. For this reason, strategies involving the use of reduced doses of thrombolytics, such as urokinase, and catheter-directed therapies have been investigated as alternatives to minimize these risks, although there is still a need for robust studies to confirm the safety and efficacy of these approaches (Khandait et al., 2023; Hobohm; Keller; Konstantinides, 2023).

For **stable** cases **(low risk)**, direct oral anticoagulants (DOACs) have advantages: they are not inferior to vitamin K antagonists (VKAs) in preventing recurrence and reduce serious bleeding events. However, they are contraindicated in severe renal failure, antiphospholipid syndrome (APS) - where AVKs are preferable - pregnancy and lactation (HOBOHM). The duration of therapy depends on the nature of the event: 3-6 months for provoked PE (recurrence rate 2.5%/year), while unprovoked PE or PE associated with permanent thrombophilia requires extended therapy (recurrence rate 4.5%/year) (Hobohm; Keller; Konstantinides, 2023).

Despite the advantages of direct oral anticoagulants (DOACs) in preventing recurrence and reducing serious bleeding events, their use is contraindicated in specific clinical situations, such as severe renal failure, antiphospholipid syndrome (especially in the triple-positive form), pregnancy and lactation, where vitamin K antagonists remain the preferred option. In addition, patients with extreme comorbidities, such as morbid obesity, require careful monitoring due to the limited evidence on the efficacy and safety of DOACs in these conditions (Khandait et al., 2023; Hobohm; Keller; Konstantinides, 2023).

During the management of PE in pregnant women, low potency anticoagulants (LWMH) are recommended as the initial therapeutic option as they cannot cross the placenta and are maintained for a period of 6 months until postpartum. An exception is vitamin K antagonists, which, although they are rarely used, are formally contraindicated only in the first trimester of pregnancy (Kulka et al., 2021).

The heterogeneity in the guidelines reflects unresolved dilemmas. **Fluid therapy in the RV** remains controversial: excess volume aggravates right heart failure, but restriction compromises cardiac output. (Khandait et al., 2023) The recommendation for individualized volume responsiveness testing lacks standardized protocols, requiring new studies.

Risk stratification in intermediate-risk PE plays a central role in therapeutic decisions and in predicting clinical outcomes. Despite initial hemodynamic stability, many patients have right ventricular dysfunction, evidenced by echocardiography or angiotomography, associated with elevated biomarkers such as troponin and BNP, which may indicate an increased risk of deterioration and early death. (Machanahalli Balakrishna et al, 2022) Guidelines such as those from the ESC and the American Heart Association recommend a multi-level approach, combining tools such as PESI/sPESI, imaging findings and laboratory markers to differentiate intermediate-high and low risk cases. (Khandait et al., 2023; Hobohm, Keller and Konstantinides, 2023) This classification allows for safer decisions regarding the

use of advanced therapies, such as systemic or catheter-directed thrombolysis, reserved for subgroups with signs of imminent decompensation. In addition, longitudinal follow-up is essential to detect possible late complications, such as chronic thromboembolic pulmonary hypertension (Kulka et al., 2021).

As for **thrombolysis at intermediate risk**, the mortality benefit of PEITHO is offset by the hemorrhagic risk. (Khandait et al., 2023) Strategies such as reduced doses of thrombolytics or catheter-directed therapies can mitigate risks, but robust evidence is still scarce. Candidate selection should integrate dynamic biomarkers, bleeding *scores* and serial echocardiographic evaluation.

DOACs have revolutionized anticoagulation, but gaps remain. Patients with triple--positive APS have therapeutic failures with rivaroxaban, requiring genotyping and individualized monitoring. (Hobohm; Keller; Konstantinides, 2023) In addition, its safety in extreme comorbidities (e.g. morbid obesity) requires investigation.

The implementation of **multidisciplinary teams (PERT)** optimizes complex decisions, especially in intermediate and high-risk cases. (Khandait et al., 2023) For refractory PE, interventions such as surgical thrombectomy or venoarterial extracorporeal membrane oxygenation (ECMO) are alternatives when thrombolysis fails, although post-thrombectomy mortality varies according to previous hemodynamic stability (7.9% without shock vs. 44.4% with cardiac arrest). (Kulka et al., 2021)

Empirical anticoagulation in suspected high probability PE (e.g. Wells score > 6) is consensual, but requires immediate assessment of the hemorrhagic risk. (Hobohm; Keller; Konstantinides, 2023; Khandait et al., 2023) In absolute contraindications, the inferior vena cava filter emerges as a transitional option. (Khandait et al., 2023), 2023) Finally, the annual reassessment of the benefit-risk ratio of prolonged anticoagulation by the attending physician is crucial to balance recurrence prevention and safety. (Hobohm; Keller; Konstantinides, 2023)

The evolution of therapeutic strategies for PE has been marked by a progressive shift from an approach based solely on systemic anticoagulation to an interventional or multidisciplinary approach. Although anticoagulation, usually initiated with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), is still the most widely used method of therapy for PE, in patients with high-risk "massive" and intermediate-high risk "submassive" PE, systemic thrombolysis - which usually accompanies the rapid dissolution of occlusive thrombi and recovery of perfusion of the lung parenchyma - is the recommended approach (Baram et al., 2020). Although systemic thrombolysis has been shown to be effective in reducing mortality in high-risk PE patients, there is still a risk of serious hemorrhagic episodes, including intracranial hemorrhages, motivating healthcare professionals to look for safer alternatives. Catheter-directed therapies (CDT) have shown promising results by reducing the administration of thrombolytic agents with a low effective concentration directly into the occlusive thrombus in percutaneous catheter implantation. DCT minimizes the systemic exposure of drugs and thus reduces bleeding complications while maintaining effective fibrinolysis (FINOCCHIARO et al., 2024; Balakrishna et al., 2022). Ultrasound-assisted CDT (USCDT) enhances the modes of action of thrombolytic therapy, with acoustic energy that increases the penetration of thrombolytic agents into the matrix to accelerate the dissolution of these occlusive ducts and improve hemodynamic parameters (CHOPARD et al, 2022; Balakrishna et al., 2022).

The impact of these diagnostic and therapeutic advances on the outcomes of PE pa-

tients has been significant. Evidence shows that short-term survival has improved, the rate of hemodynamic decompensation has decreased and long-term functional recovery has improved. The possibility of early identification of patients at high risk of deterioration and initiation of immediate aggressive therapy, which has the potential to reverse right ventricular dysfunction while irreparable damage has not yet occurred, has been a significant advance (Baram et al., 2020). The diagnostic approach to patients using clinical scores, biomarkers and advanced imaging was facilitated and enabled interventions (Baram et al., 2020). Another innovation was improved imaging techniques, which provided objective measures of clot burden and right ventricular performance that correlate closely with clinical outcomes. This has enabled doctors to modify treatment regimens based on these changes, optimizing the benefit-loss ratio and significantly reducing mortality associated with PE.

Future perspectives related to the treatment of pulmonary embolism have demonstrated the possible integration of emerging digital technologies, biomarker research and interventional refinement to further improve patient outcomes and safety. One of the areas with the greatest potential includes the use of machine learning algorithms and artificial intelligence in diagnostic imaging and risk stratification. New deep learning models are able to automatically quantify pulmonary clot burden and monitor changes in right ventricular size, providing rapid, reproducible and objective metrics that facilitate more data-driven treatment decisions compared to traditional manual methods for, as a rule, making critical clinical decisions (ISHAAYA et al, 2020; GÖTZINGER et al., 2023). In parallel, studies of new pharmacological agents that target clot-specific parts of the coagulation cascade seem to produce clinical treatment with maximum efficacy for dissolving the thrombotic clot, minimizing risks of hemorrhagic complications ("2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)", 2020; ERYTHRO-POULOU-KALTSIDOU et al., 2020). New therapies for subsequent systemic thrombolysis with a reduced dose and targeted inhibition of the action of fibrinolysis seem to be the next generation of this logic. Advances in catheter devices for mechanical thrombectomy and aspiration thrombectomy are installing technology that focuses on reducing residual clot and reducing procedure time; by the same line of logic, there is a focus on hemodynamic stability (FINOCCHIARO et al., 2024; Baram et al., 2020). In addition, the increased adoption of telemedicine and remote monitoring platforms will contribute to long-term management by enabling surveillance of adherence to anticoagulant therapy, promptly alerting recurrent thrombosis and promptly intervening on an outpatient basis as necessary. However, such digital health solutions will not only be responsible for the brief breakthrough in the field of PE, but also for improving resource utilization, reducing unplanned readmissions and automating follow-up (Khandait et al., 2023; LIEDERMAN et al., 2020). Thus, taken together, the strategies mentioned above point to a new era of PE management - one in which patient-centered care integrated with technological innovation becomes the norm, rather than the opposite.

CONCLUSION

Acute pulmonary embolism remains one of the main challenges facing contemporary medical practice, not only because of its high prevalence and potential severity, but also because of the heterogeneity of its clinical presentations and the complexities involved in its risk stratification and therapeutic approach.

Despite advances in diagnosis, especially the application of clinical scores, biomarkers and highly accurate imaging tests, the significant mortality observed, especially in patients with intermediate-risk PE, reinforces the need for rigorous clinical surveillance and therapeutic individualization.

In this scenario, the role of early assessment of right ventricular function and the rational use of biomarkers as central tools for therapeutic decisions, as recommended by international guidelines, stand out. Anticoagulation remains the mainstay of treatment at all risk levels, while thrombolysis, in its different modalities, and catheter-based reperfusion therapies are emerging as valuable options for selected subgroups, provided they are carefully indicated.

Current literature also draws attention to the importance of longitudinal post-discharge follow-up, with a view to preventing chronic complications, such as thromboembolic pulmonary hypertension, and continually reassessing the need for prolonged anticoagulation. In this context, the use of multidisciplinary teams (PERT) has shown promise, especially in more complex centers, promoting safer, evidence-based clinical decisions.

Therefore, the effective management of acute PE requires not only technical mastery and up-to-date knowledge, but also sensitivity to recognize the hidden risks in intermediate-risk cases and a care structure that favors shared decisions and early interventions. The integration of these strategies represents the most promising way to reduce the morbidity and mortality of pulmonary embolism in clinical practice.

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