



## EDITORIAL COMMENT

## Reperfusion therapy in high-risk pulmonary embolism: Underuse of a life-saving treatment is still a concern



### Terapêutica de reperfusão no tromboembolismo pulmonar agudo de alto-risco: a subutilização ainda é uma preocupação

Cátia Santos-Ferreira

Cardiology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Available online 19 December 2023

Venous thromboembolism (VTE) is the third leading cause of cardiovascular death worldwide (behind acute coronary syndrome and ischemic stroke),<sup>1</sup> and acute pulmonary embolism (PE) is responsible for most of its associated morbidity and mortality. Although the incidence of PE has increased in recent decades, this has been paralleled by a decrease in mortality.<sup>2</sup> Nevertheless, PE remains the leading preventable cause of death in hospitalized patients,<sup>3</sup> which highlights the epidemiological importance and severity of this condition.

Systemic thrombolytic therapy for acute PE has been used for more than 50 years and aims to quickly reduce the clot burden and consequently right ventricular (RV) afterload. In a meta-analysis of 15 thrombolysis trials that included (but were not restricted to) patients with acute high-risk PE (HR-PE), thrombolysis significantly reduced the combined endpoint of mortality and recurrent PE.<sup>4</sup> However, the reduction in overall mortality was not significant in hemodynamically stable patients, and an increased risk of major and intracranial bleeding was observed.<sup>4</sup>

Taking into consideration the benefit-to-risk ratio, the 2019 European Society of Cardiology PE guidelines recommend systemic thrombolysis only for treating HR-PE, defined

by the presence of cardiac arrest, obstructive shock, or hypotension (systolic blood pressure < 90 mmHg, or a systolic pressure drop of  $\geq 40$  mmHg for > 15 min if not caused by new-onset arrhythmia, hypovolemia, or sepsis).<sup>1</sup>

In this issue of the *Journal*, Martinho et al.<sup>5</sup> present a study analyzing the characteristics, comorbidities, treatment, and outcome of 74 patients admitted to a Portuguese tertiary care hospital with HR-PE between 2008 and 2018. The main objective of this retrospective study was to determine the use of systemic thrombolysis for hospitalized patients with acute PE and its possible impact on short- and long-term prognosis. In addition, the authors investigated predictors of non-reperfusion.<sup>5</sup>

The study's primary endpoint was the use of systemic thrombolysis (50% of cases), while the rate of alternative reperfusion methods was minimal (less than 2%).<sup>5</sup> The main predictors of non-reperfusion were advanced age and the presence of absolute contraindications for thrombolysis. Underuse of systemic thrombolysis in potentially eligible HR-PE patients has been similarly reported in contemporary cohorts, such as the RIETE registry (reperfusion therapy used in 20% of HR-PE patients)<sup>6</sup> and German nationwide data (thrombolytic therapy used in 50% of HR-PE patients).<sup>3</sup>

Another important finding of Martinho et al.'s study<sup>5</sup> is the reduction of 30-day (17.1% vs. 40.5%,  $p = 0.052$ ) and long-term mortality (51.4% vs. 81.1%,  $p = 0.005$ ) in HR-PE patients who received thrombolysis compared to those without this reperfusion therapy. Conversely, there was a tendency (not

DOI of original article: <https://doi.org/10.1016/j.repc.2023.07.005>

E-mail address: [catiaspferreira@hotmail.com](mailto:catiaspferreira@hotmail.com)

<https://doi.org/10.1016/j.repc.2023.12.001>

0870-2551/© 2023 Published by Elsevier España, S.L.U. on behalf of Sociedade Portuguesa de Cardiologia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

statistically significant, probably due to lack of power to detect a difference) for a higher risk of bleeding events among HR-PE patients who received reperfusion therapy compared to those who did not receive reperfusion.

Reluctance to use systemic thrombolysis in the real world is a serious concern and was one of the potential explanations identified for the recently observed trend of increasing mortality in HR-PE in the US population.<sup>7</sup> Besides advanced age and medical comorbidities in hospitalized patients with PE, the underuse of systemic thrombolysis may also be explained by the risk of cerebral hemorrhage, and the overall lack of experience in the use of thrombolytic agents in the era of primary percutaneous revascularization for ST-elevation myocardial infarction.<sup>8</sup>

Although systemic thrombolysis remains the reperfusion technique with the highest level of evidence (class I, level of evidence B), alternative reperfusion methods should be considered in those with an excessive risk of bleeding, contraindication for systemic thrombolysis, or failed thrombolysis.<sup>1</sup> Surgical embolectomy (class I, level C), performed with cardiopulmonary bypass without aortic clamping and circulatory arrest, is not widely available in the emergency setting in Portugal, as pointed out by the authors. Catheter-directed interventions (class IIa, level C) add new treatment options, more specific than systemic thrombolysis and less invasive than surgical embolectomy, and are becoming a particularly attractive reperfusion strategy.

Different types of catheters are used for mechanical fragmentation, thrombus aspiration, or more frequently a pharmacomechanical approach that combines mechanical or ultrasound fragmentation of the thrombus with in-situ reduced-dose thrombolysis.<sup>1</sup> Promising results with high procedural success rates (87%) and with improvement in RV function, especially with a pharmacomechanical approach, have been seen in cohort studies and small randomized trials.<sup>1</sup> Of note, bleeding complications are far from being eliminated using catheter-directed thrombolysis, so aspiration thrombectomy has an obvious potential advantage in patients with a high bleeding risk because no thrombolytic drugs are required.<sup>9</sup> Nevertheless, large randomized comparative trials that are powerful enough to assess the clinical efficacy of catheter-based interventions are lacking. Finally, the asymmetrical access to catheter-based interventions in Portugal should not be forgotten, highlighting the need for the establishment of PE response teams and systems of care for HR-PE at regional and national levels.<sup>1,10</sup>

Lastly, PE causes not only death but also sustained morbidity through diseases such as post-PE syndrome and chronic thromboembolic pulmonary hypertension. Although it remains unclear whether early reperfusion therapy prevents long-term complications,<sup>1</sup> Martinho et al.<sup>5</sup> reveal an encouraging long-term reduction in the combined endpoint of cardiovascular mortality, embolic recurrence, and occurrence of chronic thromboembolic pulmonary hypertension in HR-PE patients who received reperfusion therapy compared to those who did not (59.5% vs. 86.5%,  $p = 0.005$ ).

As pointed out by the authors, the study has several limitations due to its retrospective, observational,

and single-center design. Firstly, the small sample, missing information, and possible errors in coding diagnostics and treatments reduce the statistical power of the analysis and are sources of bias. Secondly, the data may not be generalizable to the national level. Lastly, its non-randomized nature may lead to a significant selection bias, which possibly overestimates the positive impact of thrombolysis therapy. However, from my standpoint, the authors should be commended for reporting for the first time the reperfusion rate in HR-PE in a Portuguese tertiary center.

In summary, the relevance of Martinho et al.'s study includes their characterization of a contemporary real-world HR-PE population and they confirm the underuse of systemic thrombolysis, a first-line and life-saving reperfusion therapy. Furthermore, alternative reperfusion methods are also largely underused in this population. This reveals a need for proper implementation of the PE guideline recommendations on the appropriate use of reperfusion methods in HR-PE patients in Portugal.

## Conflicts of interest

The author has no conflicts of interest to declare.

## References

1. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41:543–603.
2. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000–15: analysis of vital registration data from the WHO Mortality Database. *Lancet Respir Med*. 2020;8:277–87.
3. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. *Eur Heart J*. 2020;41:522–9.
4. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J*. 2015;36:605–14.
5. Martinho M, Calé R, Santos JG, et al. Underuse of reperfusion therapy with systemic thrombolysis in high-risk acute pulmonary embolism in a Portuguese center. *Rev Port Cardiol*. 2023; S0870-2551(23)00458-4.
6. Jiménez D, Bikdeli B, Barrios D, et al. Epidemiology, patterns of care and mortality for patients with hemodynamically unstable acute symptomatic pulmonary embolism. *Int J Cardiol*. 2018;269:327–33.
7. Zuin M, Bikdeli B, Davies J, et al. Contemporary trends in mortality related to high-risk pulmonary embolism in US from 1999 to 2019. *Thromb Res*. 2023;228:72–80.
8. Palazzini M, Dardi F, Magnani I, et al. Progress in the treatment of acute pulmonary embolism and chronic thrombo-embolic pulmonary hypertension/disease. *Eur Heart J Suppl*. 2023;25 Suppl. B:B90–4.
9. Götzinger F, Lauder L, Sharp ASP, et al. Interventional therapies for pulmonary embolism. *Nat Rev Cardiol*. 2023;20:670–84.
10. Calé R, Pereira H, Ferreira F, et al. Blueprint for developing an effective pulmonary embolism response network. *Rev Port Cardiol*. 2023;42:491–501.