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EDITORIAL COMMENT

Catheter-directed therapy for acute pulmonary embolism: Time for ''debulking and extracting'' the gaps

Tratamento dirigido por cateter na embolia pulmonar aguda: tempo para extrair as lacunas na evidência

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Compared with recent advances in the treatment of acute cardiovascular diseases, such as myocardial infarction and stroke, the treatment and outcome of pulmonary embolism (PE) have remained relatively unchanged over the last two decades.[1] Despite high fatality, most patients continue to be treated conservatively with anticoagulation alone facing the challenge of undergoing the still doubtful optimal therapeutic strategy, under a broad umbrella of risks and benefits. Moreover, patients who survive an acute episode often experience long term complications including pulmonary hypertension, dyspnea, exercise intolerance and reduced quality of life.[2] These concerns have driven several experts to call for the formation of multidisciplinary PE response teams (PERT) to discuss treatment options and provide immediate advice and therapy for patients with acute PE. In this context, catheter-directed therapy (CDT), including catheter-directed fibrinolysis (CDF) and percutaneous mechanical aspiration have emerged as a potentially powerful and safer alternative to systemic fibrinolysis.[3] The goals include rapid reduction in pulmonary artery pressure, right ventricular strain and pulmonary vascular resistance with a presumable decrease in clinical deterioration risk and eventually death.

In this issue of the Journal, Calé et al.[4] report the first Portuguese experience of a single center in CDT for acute PE at higher risk by exploring the safety and efficacy of this approach. The authors retrospectively included 29 consecutive patients with intermediate-high (51.7%) and high risk (48.3%) acute PE treated with Indigo® mechanical thrombectomy system with or without CDF, pursuing a rigorous analysis of their experience with appropriate diagnostic imaging, invasive hemodynamic and short-term follow-up clinical recordings. The reported technical and clinical successes were 96.6% and 75.9%, respectively, with acceptable safety in the assessment of patients' baseline characteristics.

This study[4] provides a clear picture of the successful inception of a PERT in the national territory. Nevertheless, in line with previous reports, these findings need to be

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interpreted with caution, considering not only the limited sample size and uncontrolled nature, but especially the controversial decisions about patient selection for CDT among intermediate-risk populations, in whom there are closely counterbalanced hazards and benefits to the procedure.

Studies such as SEATTLE II[5] and OPTALYSE[6] have been notable in demonstrating the feasibility of using CDF to improve outcomes in acute PE. Although demonstrating a significant reduction in right ventricular (RV) dysfunction, they also reported a non-neglectable major bleeding rate, leading to an increased focus on the development of mechanical thrombectomy.

The EXTRACT-PE[7] is the latest trial examining mechanical thrombectomy in patients with acute PE and RV dysfunction (considered submassive by American Heart Association guidelines[8]) through a prospective, single-arm trial designed to assess the safety and efficacy of the same thrombectomy system used by Calé et al.[4] in 119 patients. The trial was conducted properly and can be compared with the FLARE,[9] a single-arm trial assessing the FlowTriever system in 106 patients with acute PE. Both studies demonstrated comparable clinical efficacy through a popular surrogate endpoint – reduction in the RV/LV ratio – at 48 h of follow-up. At this point, it should be noted that selecting the reliable metrics for positive outcomes in CDT is still a cause of some trouble. Calé et al.[4] defined clinical success as any improvement in hemodynamic and oxygenation parameters, pulmonary hypertension or RV strain at 48 hours, and survival to hospital discharge, eventually translating into clinically meaningful endpoints for patients. The use of the RV/LV ratio has been widely studied as a prognostic marker in PE.[10] However, its use as a surrogate efficacy endpoint has not been rigorously assessed as an appropriate measurement for intervention outcomes. Improvement in PE-related mortality is likely not reflected by a reduction in the RV/LV ratio, proven by the fact that patients with submassive PE are by definition normotensive. Reported mortality rates are low in this group. Given the distinct definitions of clinical success, the results from studies are sometimes barely comparable, especially among transatlantic scenarios. Rates of major adverse events (1.7% vs. 3.8%) and major bleeding (1.7% vs. 1%) were similar for the EXTRACT-PE and FLARE trials, respectively. However, it should be noted that both studies included a significant number of patients with a simplified PE severity index of 0 (46.2% in the EXTRACT-PE and 55.8% in the FLARE). These patients have been shown to have a mortality of $\leq$1% at 30 days.[8] Additionally, most subjects in both studies had an elevation of at least one biomarker, although some data suggest that biomarkers may have a limited value in predicting mortality in normotensive patients. On the contrary, the study by Calé et al.[4] included a residual number of patients with a simplified PE severity index of 0 (3.4%), explained by a baseline critical condition due to PE severity and/or comorbidities in this cohort, jeopardizing any comparison between major adverse events and major bleeding. Nevertheless, the study[4] described no major bleeding and reported a major adverse events rate within 48 hours of 10.3%. Also, the authors found an average reduction of 16.1% in systolic pulmonary artery pressure (PAP) and 15.5% in mean PAP, achieved with 86.2% of patients receiving no fibrinolysis. These immediate hemodynamic results are quite good, compared with data of the EXTRACT-PE (8.7% reduction of systolic PAP) and FLARE (6.7% reduction of mean PAP).

Despite the resemblances in design and accumulation of data from several independently conducted trials in this area, important shortcomings in our understanding of CDT remain:

- Firstly, the measurement of outcomes with validated clinical impact – there is a need to refocus our goals on better-combined improvements in surrogate endpoints in the demonstration of acute changes in clinically meaningful parameters and long term demonstration of benefits.[8] Indeed, one of the main caveats raised by the present study[4] is whether the percutaneous approach will evolve to become the preferred strategy in intermediate-high risk cases over anticoagulation alone. To answer this question, refining the stratification model of this heterogenous population will need to be addressed.
- Secondly, the likelihood of significant variability in operator-technique performance – unlike other vascular beds, subtotal thrombectomy of the pulmonary vessels is not achievable in most cases. Rather, operator judgment determines when the CDT should be terminated, potentially impacting and confounding outcomes. ''On-table'' hemodynamic or imaging endpoints are awaiting validation to provide guidance, thereby potentially raising confidence in the therapeutic value of the procedure and improving its safety profile.

The field of percutaneous interventions for acute PE is in its early days. Tailoring the decision to pursue CDT on factors that go beyond currently accepted risk stratification schemes is a work in progress and requires further investigation. Although several questions remain, the future of CDT seems heartening.

Conflicts of interest

The author has no conflicts of interest to declare.

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