Functional limitation and right ventricular dysfunction at 6-month follow-up in patients with non-massive pulmonary embolism: useful outcomes for testing therapy of acute submassive pulmonary embolism?

Vittorio Palmieri*, Emiliano Antonio Palmieri and Aldo Celentano

Unit of Cardiology, 'Ospedale dei Pellegrini', ASL NA1, Naples, Italy

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This editorial refers to 'Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients' by B.G. Stevinson et al., on page 2517

Acute pulmonary embolism (PE) is a syndrome with a significant annual incidence, potentially associated with an elevated mortality rate.1 Patients presenting with acute PE and persistent systemic hypotension, cardiogenic shock, or cardiac arrest are classified as having massive PE; in the absence of haemodynamic instability, PE is defined generically as non-massive. The latter, however, is classified as sub-massive acute PE in the presence of right ventricular (RV) dysfunction,1 to indicate that patients with normotensive acute PE and RV dysfunction may suddenly need escalation of therapy (vasopressor and/or inotropic support, rescue fibrinolysis, cardiopulmonary resuscitation).

While clinical manifestation of acute PE may vary widely and significantly between patients, acute RV dysfunction is more quantifiable and uniform objective information in PE with relation to the severity of pulmonary vascular impairment.5 RV failure is the prominent cause of death in acute PE. This is further supported by the fact that in the setting of non-massive acute PE, RV dysfunction correlates with brain natriuretic peptide and troponins, which are in turn biomarkers of the severity of RV overload,6 providing additional information for risk stratification of the heterogeneous group of patients with normotensive PE.7–11 However, whether aggressive treatment (i.e. fibrinolysis or catheter-based pulmonary embolectomy) should be employed in acute submassive PE in addition to anticoagulation is controversial.1 In fact, while fibrinolysis or thromboembolectomy are associated with partial recovery of RV dysfunction,12 there is non-conclusive evidence of the superiority of fibrinolysis over anticoagulation alone. The only randomized controlled study available in acute submassive PE found that alteplase was associated with a reduction in the need for rescue fibrinolysis, which, however, did not impact significantly on the 30 day mortality rate.13 The impact of fibrinolysis in submassive PE on long-term prevention of persistent RV dysfunction, pulmonary hypertension, and quality of life is less well established. To this extent, it appears a logical approach to assess long-term outcome related to RV dysfunction for assessment of the global impact of acute management of submassive PE.

Stevinson et al.14 showed that at 6-month follow-up, a significant proportion (41%) of previously healthy patients with first-time non-massive PE (50% with submassive PE) had functional limitation [i.e. a 6-min walk test (6MWT) <330 m or NYHA class >2] or echocardiographic RV dysfunction.14 Therefore, functional limitation and/or RV dysfunction at 6-month follow-up are proposed as additive endpoints to be accounted for in treatment studies of PE.

Does this study provide useful information for better understanding of the natural history of non-massive PE? No doubt. Is the information provided by this study14 really useful to re-think studies on treatment of submassive PE? Hardly.

First, all patients evaluated by Stevinson et al.14 were previously healthy. While such a peculiarity of the study is used to reinforce the relevance of the outcome at 6-month follow-up, it also represents an intrinsic limitation of the study, because the study sample does not fully represent the population of patients with PE, who most often are affected by co-morbidity; thus, the results of the study cannot be generalized. However, and importantly, the truth is that RV dysfunction and functional limitation may be even more incident in unselected patients surviving to acute submassive PE, with a potentially significant impact of the disability on public health and general welfare.

Secondly, in the study by Stevinson et al.,14 echocardiographic RV dysfunction at baseline performed poorly in predicting the composite outcome at 6 months. The authors stressed that for identification of the outcome at 6-month follow-up (abnormal functional capacity and/or RV dysfunction) accuracy was higher with RV hypokinesis at baseline than with RV dilatation or estimated pulmonary pressure above 40 mmHg. Notwithstanding this, the positive
predictive value associated with acute RV hypokinesis for identification of ‘pulmonary problems’ at 6-month follow-up was only 26%. Only nine patients (33%) had functional limitation among the 27 with RV dysfunction at 6-month follow-up, whereas functional limitation was reported in 18 patients among those without RV dysfunction at 6 months (18/52, 22%); therefore, there was no clinically significant concordance between RV dysfunction and functional limitation at 6-month follow-up. Therefore, in a clinical scenario in single patients, RV hypokinesis or RV dilatation at rest at the diagnosis of non-massive PE does not appear to be a reliable indicator of outcome at 6 months. Conversely, the data of Stevinson et al. showed that the absence of RV dysfunction may really predict a benign clinical course with a specificity of 80%, reinforcing previous data. On the other hand, the study by Stevinson et al. may be affected by the survival effect. The authors only evaluated survivors to acute submassive PE, and recorded four PE event. Later, mortality tended to reach a plateau after between the third and the fourth week following the acute trend of the mortality rate, with a first significant peak with non-massive PE, and tend to show a bimodal temporal distribution of the pulmonary vascular bed are more likely to present limitation at 6-month follow-up. Therefore, in a clinical setting of submassive PE may impact on long-term mortality remains an unresolved issue.

While 41% of patients had ‘cardiopulmonary problems’ at 6-month follow-up, only 20% of the study sample actually expressed some index of poor quality of life. ‘feeling unable to do the shopping’ most often identified poor quality of life, whereas only 8% of the patients evaluated in the study had both RV dysfunction and functional limitation. Whether ‘feeling unable to do the shopping’ may be considered as a reliable index of functional limitation is unclear; on the other hand, in the study population, 87% reported improved health status after the hospitalization for PE. Therefore, treatment strategies having resolution of acute RV dysfunction as the therapeutic target in acute PE should be evaluated against short-term end-points. In this regard, assessment of troponins11,15,18,19 and of brain natriuretic peptide20 may be useful to refine prognostic stratification of submassive acute PE by contributing to the identification of patients in whom the short- and long-term benefit of fibrinolysis or catheter-based embolectomy may be superior to risks of treatment. Nevertheless, the pathophysiologic relationship between acute management of submassive PE vs. long-term persistent RV dysfunction and functional disability in submassive PE remains to be clarified in large randomized controlled trials.

Conflict of interest: none declared.

References