International Journal of Cardiology 197 (2015) 162–163

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Risk stratification of normotensive pulmonary embolism based on the sPESI — Does it work for all patients?

Kristian Hellenkamp [a,1], Anja Kaeberich [b,1], Johanna Schwung [a], Stavros Konstantinides [b], Mareike Lankeit [a,b,*]

[a] Clinic of Cardiology and Pneumology, Heart Center, Georg-August University of Göttingen, Germany
[b] Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Johannes Gutenberg-University Mainz, Germany

ARTICLE INFO

Article history:
Received 5 June 2015
Accepted 20 June 2015
Available online 27 June 2015

In normotensive patients with confirmed pulmonary embolism (PE), the 2014 ESC guideline proposes risk stratification to guide risk-adapted management and treatment decisions [1]. Depending on the attributed risk for an adverse clinical course, treatment options range from home treatment of *low-risk* patients to monitoring and possibly rescue thrombolysis if clinical signs of hemodynamic decompensation become present in *intermediate-high-risk* patients. We present here a case, revealing that appropriate risk assessment of both – PE-related risk and bleeding risk – is still challenging.

A 76 year old female patient presented to the emergency unit with cough since two weeks, chest pain and exertional dyspnea which had started four days earlier. Apart from a history of deep vein thrombosis and several gynecological operations, the patient did not have any relevant comorbidities. Her medication included amitriptyline and aspirin. On admission, the patient presented with a blood pressure of 145/90 mm Hg, a heart rate of 90 beats per minute, respiration rate of 30 per minute and a resting oxygen saturation of 92% while breathing room air. Electrocardiogram did not reveal abnormal findings. Routine laboratory testing showed a mild thrombocytopenia (123,000/μl) and a slightly reduced glomerular filtration rate (GFR, 59 ml/min/1.73 m^2). Based on the Wells prediction rule indicating an intermediate probability of PE, D-dimer testing was performed (12.5 mg/l) followed by multidetector computed tomography (MDCT) showing central bilateral thrombi in the pulmonary arteries (Fig. 1A). Additionally, right ventricular (RV) dilatation was detected (Fig. 1B) and subsequently performed transthoracic echocardiography (TTE) confirmed the presence of RV dysfunction (indicated by RV dilatation, paradoxical septal motion and an estimated systolic pulmonary arterial pressure of 46 mm Hg). Moreover, laboratory testing showed elevated plasma concentrations of high-sensitivity troponin T (hsTnT, 65.8 ng/l; reference <14 ng/l [2]) and N-terminal pro-brain natriuretic peptide (NT-proBNP, 9024 pg/ml; reference <600 pg/ml [3]). Since the patient met all inclusion and no exclusion criteria, she was included in the Pulmonary Embolism Thrombolysis (PEITHO) study [4] and randomized to tenecteplase versus placebo on top on therapeutic anticoagulation using unfractionated heparin. On the second day of hospitalization, the patient developed a right-sided hemiparesis and paresthesia. Cranial CT revealed intracranial bleeding in the left hemisphere (Fig. 1C). The patient recovered with moderate disability (Rankin score, 3 points [5]) and was discharged on day 22 to a rehabilitation clinic. Anticoagulant treatment on discharge consisted of phenprocoumon (target INR, 2.0–3.0).

According to the 2014 ESC guideline, stepwise risk assessment in patients with confirmed normotensive PE, should be started with a validated clinical risk prediction score, preferably the Pulmonary Embolism Severity Index (PESI) or its simplified version (sPESI) [6], to distinguish between *low-* and *intermediate-risk* patients [1]. Reflecting the absence of relevant comorbidities and stable hemodynamics on admission, the sPESI was calculated post-hoc with 0 points in the presented case. Since a sPESI of 0 has been shown to be at least as accurate as imaging parameters and biomarkers for the identification of patients at *low-risk* [6,7], routine performance of imaging or laboratory tests is not considered necessary in those patients [1]. However, based on the sPESI alone, the presented patient would have been presumably falsely classified as *low-risk*. According to the ESC guideline, patients with a sPESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction (e. g., in situations in which imaging or biomarker results become available before calculation of the clinical prognostic score), should be classified in the *intermediate-low-risk* category [1]. However, given the combination of i) RV dilatation on MDCT, ii) confirmation of RV dysfunction on TTE and iii) elevation of biomarkers of myocardial ischemia (hsTnT) and dysfunction (NT-proBNP) in the presented case, this patient might have been classified more appropriately as *intermediate-high-risk*. A recommendation referring to this combination is missing in the 2014 ESC guideline and the optimal treatment strategy remains unclear.

Recently developed and validated risk prediction scores such as the Bova score [8] are based on the combination of clinical parameters and tests indicating RV dysfunction. These scores may be more useful for the identification of a patient subgroup with a higher risk

* Corresponding author at: Center for Thrombosis and Hemostasis (CTH), University Medical Center Mainz, Johannes Gutenberg University of Mainz, Langenbeckstraße 1, 55131 Mainz, Germany.
E-mail address: mareike.lankeit@unimedizin-mainz.de (M. Lankeit).
[1] The authors contributed equally.

http://dx.doi.org/10.1016/j.ijcard.2015.06.065

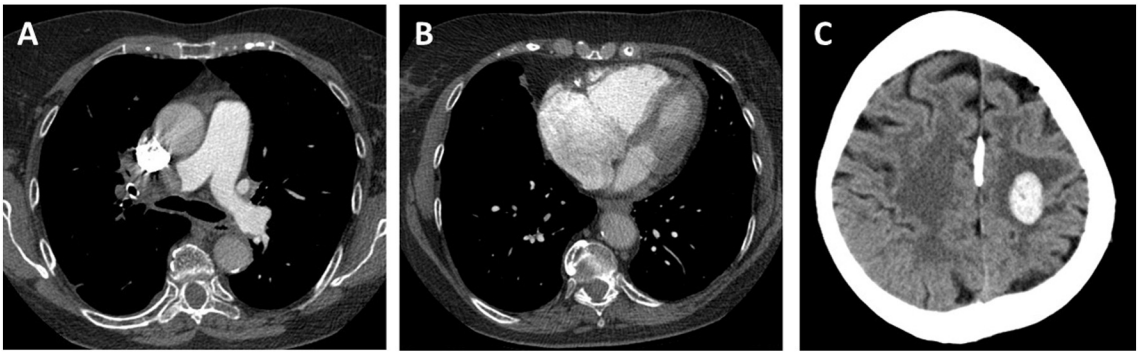

Fig. 1. CT revealing central thrombus in the right pulmonary artery (A), RV dilatation (B) and intracranial bleeding (C). Contrast-enhanced CT showing a central thrombus in the right pulmonary artery (A) and dilatation of the right atrium and ventricle compared to the left atrium and ventricle (B). (C) Cranial CT revealed intracranial bleeding in the left hemisphere sized 2.2 × 1.4 cm.

(30-day PE-related complications, 29.2% for the Bova [8]). However, whether these scores might help in guiding therapeutic decision making requires further investigation and clinical management trials.

The PEITHO study [4] has demonstrated that normotensive PE patients with evidence of RV dysfunction and elevated troponin levels benefit from thrombolytic therapy indicated by a significant reduction of the primary endpoint (death or hemodynamic decompensation within 7 days) in the tenecteplase group compared to placebo (OR, 0.44; 95% CI, 0.23–0.87; $p = 0.015$). However, this benefit was counterbalanced by a significant increase of major hemorrhage (6.3 vs. 1.2% major extracranial bleeding, $p < 0.001$ and 2.4 vs. 0.2% stroke, $p = 0.003$) as in the presented case. Therefore, routine use of thrombolytic therapy is not recommended in normotensive patients but (rescue) thrombolysis should be considered for patients with *intermediate-high-risk* and clinical signs of hemodynamic decompensation [1]. Although not unblinded from study medication, based on the occurrence of intracranial bleeding in the presented case, the patient presumably received verum. While no contraindications for systemic thrombolysis were present, several potential risk factors for bleeding could be identified: female sex, age (76 years), mild thrombocytopenia, mild renal insufficiency, and aspirin intake. In the PEITHO study, patients aged ≥75 years tended to have an increased rate of major extracranial bleeding compared to younger patients, although this effect did not reach statistical significance [4]. Unfortunately, reliable and validated tools for the prediction of bleeding risk in patients with acute PE – both, for patients receiving thrombolysis and for patients receiving anticoagulation only [9] – are still missing.

In conclusion, the sPESI is generally very reliable in identifying normotensive patients with acute PE and a *low-risk* of an adverse outcome. However and as presented in this case, the presence of RV dysfunction on diagnostic MDCT should prompt further prognostic assessment and classification into the *intermediate-high-* versus *intermediate-low-risk* category, even if the sPESI is 0. Additionally, the optimal tools to assess the risk-to-benefit ratio of thrombolytic therapy in normotensive PE patients deserve further investigation.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

We thank Prof. Dr. Joachim Lotz, Department of Diagnostic and Interventional Radiology, Georg-August University of Göttingen, Germany and German Centre for Cardiovascular Research (DZHK), partner site Göttingen for images shown in Fig. 1.

The study was supported by the German Federal Ministry of Education and Research (BMBF 01EO1003). The authors are responsible for the contents of this publication.

References

[1] S.V. Konstantinides, A. Torbicki, G. Agnelli, et al., ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 35 (43) (2014) 3033–3069 (3069a–3069k).
[2] M. Lankeit, D. Jiménez, M. Kostrubiec, et al., Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study, Circulation 124 (24) (2011) 2716–2724.
[3] M. Lankeit, D. Jiménez, M. Kostrubiec, et al., Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism, Eur. Respir. J. 43 (6) (2014) 1669–1677.
[4] G. Meyer, E. Vicaut, T. Danays, et al., Fibrinolysis for patients with intermediate-risk pulmonary embolism, N. Engl. J. Med. 370 (15) (2014) 1402–1411.
[5] J. Rankin, Cerebral vascular accidents in patients over the age of 60. II. Prognosis, Scott. Med. J. 2 (5) (1957) 200–215.
[6] D. Jiménez, D. Aujesky, L. Moores, et al., Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism, Arch. Intern. Med. 170 (15) (2010) 1383–1389.
[7] M. Righini, P.M. Roy, G. Meyer, et al., The Simplified Pulmonary Embolism Severity Index (PESI): validation of a clinical prognostic model for pulmonary embolism, J. Thromb. Haemost. 9 (10) (2011) 2115–2117.
[8] C. Bova, O. Sanchez, P. Prandoni, et al., Identification of intermediate-risk patients with acute symptomatic pulmonary embolism, Eur. Respir. J. 44 (3) (2014) 694–703.
[9] F.A. Klok, J. Kooiman, M.V. Huisman, et al., Predicting anticoagulant-related bleeding in patients with venous thromboembolism: a clinically oriented review, Eur. Respir. J. 45 (1) (2015) 201–210.