Case Report

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Physiologically Guided Thrombolysis in Pulmonary Embolism

Philippe Rola[1], Michael Pratte[2], Hussein Fadlallah[3], Claire Braaten[4] and Ian Ajmo[5]

[1]Intensive Care Unit Chief of Service, Santa Cabrini Hospital, Montreal, Quebec, Canada
[2]Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[3]Cardiology Chief of Service, Santa Cabrini Hospital, Montreal, Quebec, Canada
[4]Department of Physiology, McGill University, Montreal, Quebec, Canada
[5]Intensive Care Unit, Santa Cabrini Hospital, Montreal, Quebec, Canada

We describe the case of a 69-year-old woman who presented with submassive pulmonary embolism without overt shock, but with significant signs of right ventricular failure and dyspnea on minimal exertion. She was managed using a point-of-care ultrasound and pulmonary artery pressure-guided approach in order to minimize total thrombolytic dose while nonetheless achieving significant physiological improvement.

Keywords: *POCUS; Pulmonary Embolism; Thrombolysis; Pulmonary Artery Catheter*

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INTRODUCTION

While the management of pulmonary embolism (PE) with obstructive shock clearly involves aggressive intervention, that of patients with high symptom burden without overt shock is less clear. A significant proportion of these patients who have large PEs treated conservatively may end up with post-PE syndromes including the most severe form, chronic thromboembolic pulmonary hypertension (CTEPH) [1]. There are a number of existing therapeutic options, from simple anticoagulation therapy and thrombolysis to the more recent mechanical clot aspiration and catheter-directed thrombolysis. In addition, the optimal dose for thrombolytic therapy remains unclear [2]. Here, we describe the case of a woman presenting with bilateral submassive PEs with significant symptoms who was managed with serial assessments of her physiologic parameters to guide thrombolysis and minimize adverse effects.

Corresponding author:
Philippe Rola, Intensive Care Unit Chief of Service, Santa Cabrini Hospital, Montreal, Quebec, Canada.
Email: philipperola@gmail.com

CASE REPORT

A 69-year-old woman presented to our community hospital with dyspnea and hypoxia. She was known for type II diabetes mellitus and hypertension, but otherwise quite active in daily life. On examination, she was in no apparent distress, with an oxygen saturation of 97% on 2 L/min nasal prongs. Her blood pressure was 110/82 mmHg, heart rate 94 beats per minute, and respiratory rate 26 breaths per minute. Her extremities were warm and perfused, and capillary refill time was slightly above 3 seconds. She was mentating well and the remainder of the physical examination was unremarkable. A computed tomography (CT) scan at presentation demonstrated bilateral submassive PE (Figure 1). Given these findings, the critical care team was consulted for further management and admission.

Point-of-care ultrasound (POCUS) by the critical care team showed several signs of hemodynamically significant PE, including a plethoric inferior vena cava (IVC) 23 mm in diameter, a right ventricle (RV)-to-left ventricle (LV) ratio greater than 1, the presence of the McConnell sign, as well as septal dyskinesia and a tricuspid annular plane systolic excursion (TAPSE) of 16 mm. The right ventricular outflow tract Doppler pattern was type III with early systolic notching and a "spike and ball" pattern, with an acceleration time of 80 ms. Using tricuspid regurgitant jet Doppler, pulmonary artery pressure (PAP) was estimated to be around 50 mmHg (Figures 2 and 3). An occlusive deep vein thrombosis in the right superficial femoral extending to the common femoral vein was found.

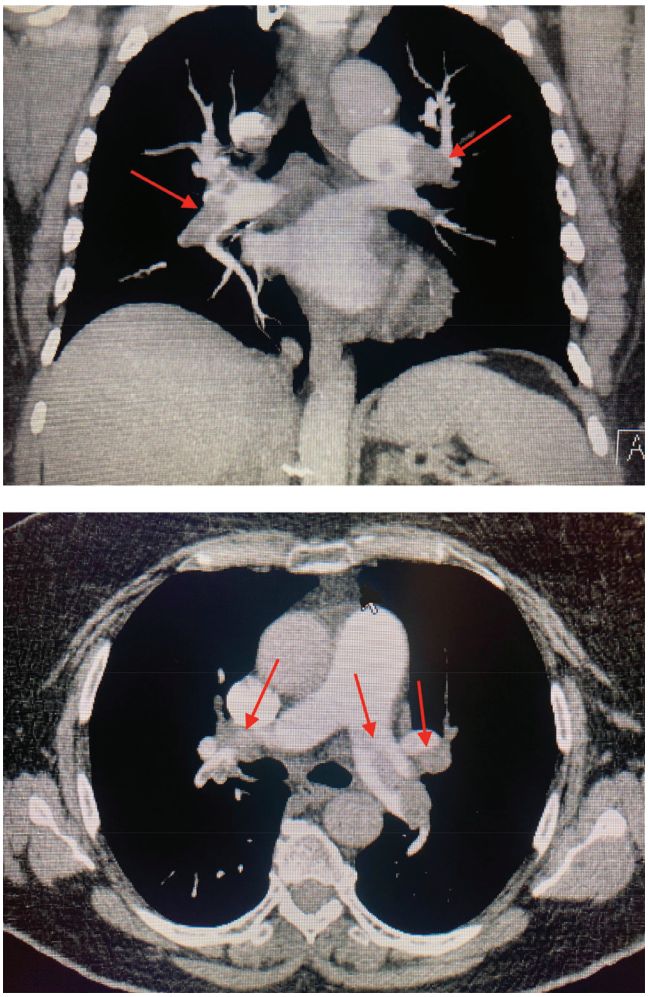

Figure 1 Computerized tomography scan showing occlusive pulmonary emboli (red arrows).

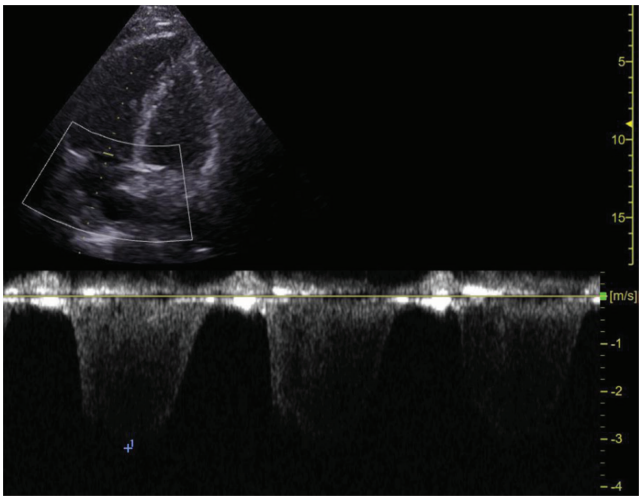

Figure 2 Apical 4 chamber view showing dilated RV and increased RV-to-LV ratio with a peak tricuspid regurgitation envelope maximum velocity (TRVmax) over 3 m/s.

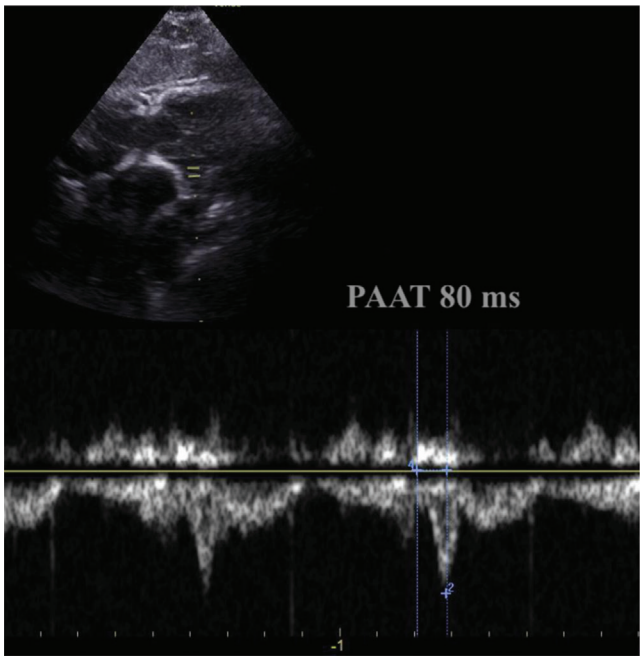

Figure 3 Right ventricular outflow tract Doppler pre-lytic therapy, showing a "spike and ball" pattern with a low pulmonary acceleration time (PAAT) of 80 ms.

Following discussion with the patient and with the cardiology service, it was decided to offer the patient more aggressive therapy with thrombolysis in hopes of reversing right ventricular dysfunction and aiding in the avoidance of potential post-PE syndromes. Informed consent was obtained after explanation of the risks involved.

The patient was admitted to the intensive care unit and a pulmonary artery (PA) catheter was placed with an initial PAP of 51/22 mmHg and central venous pressure (CVP) of 10 mmHg, yielding a PA pulsatility index (PAPi) of 2.9 and a TAPSE/pulmonary artery systolic pressure (PASP) ratio of 0.31. A bolus of 10 mg tissue plasminogen activator (tPA) was given, followed by an infusion of 1 mg/h in the PA catheter. Six hours later, the PAP was 41/16 mmHg and CVP 6 mmHg (PAPi of 4.2). Twenty hours later, there was a significant improvement in PAP at 37/14 mmHg and CVP of 2 mmHg (PAPi > 10). The decision was taken to stop the tPA infusion due to therapeutic success, having given a total of 31 mg. Following this, the patient was weaned off oxygen with complete resolution of her symptoms of dyspnea on exertion. She had a formal echocardiogram on day 3 of admission which showed normal biventricular function and a PAP of approximately 38 mmHg. She was discharged on the fourth day, and followed up 6 weeks later as an outpatient, at which time she was asymptomatic and had resumed her normal activities. Her POCUS examination at that point revealed normal RV dimensions, a TAPSE of 24 mm and a near-normal RV outflow tract Doppler envelope (Figure 4).

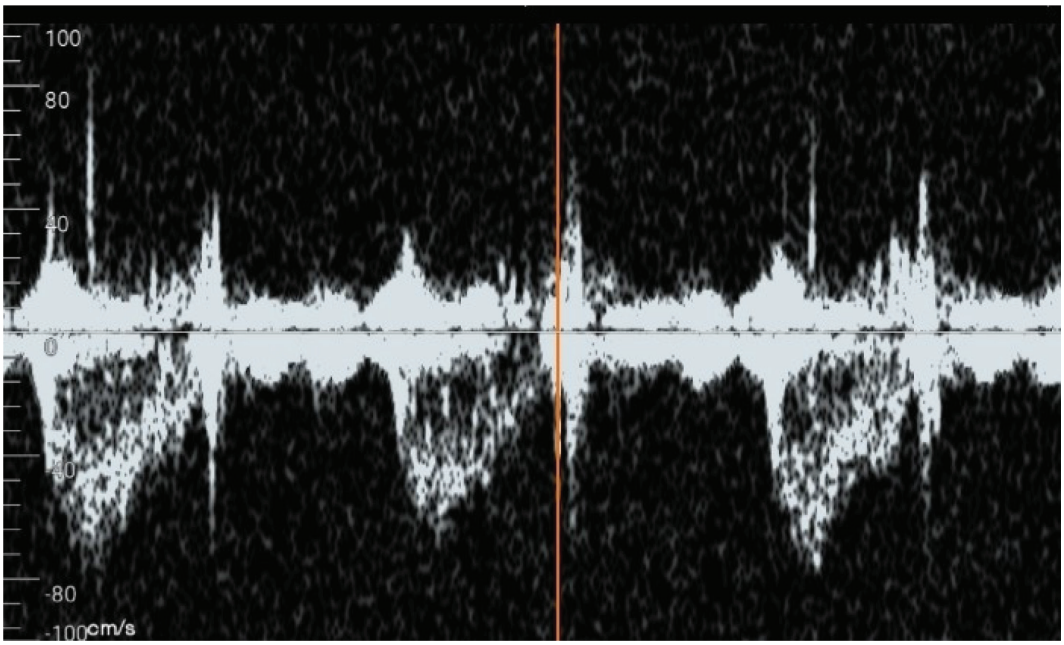

Figure 4 Right ventricular outflow tract Doppler at outpatient follow-up 6 weeks post-discharge showing much improved envelope.

Ethical Approval and Informed Consent

Ethical approval to report these cases was given by the patient herself. Written informed consent was obtained from the patient herself.

DISCUSSION

Current guidelines by the European Society of Cardiology (ESC) recommend risk stratification of acute PE into low, intermediate-low, intermediate-high, and high risk to guide treatment [3]. While the management of low- and high-risk PEs is relatively straightforward, the optimal management of intermediate-risk patients that appear hemodynamically stable with physiologically significant PE is less clear; this category can include patients with essentially normal or near-normal RV function as well as those where it is maximally strained to maintain normal vital signs. Most of the large studies seeking to risk-stratify patients presenting with PE have little or no data assessing dynamic right ventricular function, particularly in terms of ventriculo-arterial (V-A) coupling.

Echocardiographic findings associated with acute PE include RV dilatation, McConnell's sign, and decreased TAPSE [4]. Although studies have shown a negative predictive value of only 40–50% in the workup of acute PE via echocardiography [5], it remains very useful in prognostication. A study by Pruszczyk et al. found an abnormal RV-to-LV ratio yielded a hazard ratio of 7.3 for acute PE-related mortality or thrombolysis; likewise, TAPSE was found to be an independent predictor of 30-day mortality or thrombolysis [6]. RV dysfunction, on the other hand, had a relative risk of 2.4 for predicting mortality in a systematic review of echocardiography in acute PE [7]. Pulmonary arterial pressure during and following acute PE has also demonstrated prognostic utility. Elevated mean PAP at the time of PE diagnosis is independently associated with mortality and a higher prevalence of CTEPH [8, 9]. Indeed, Guerin et al. found dramatic elevations in systolic PAP (75 ± 20 mmHg) at the time of PE diagnosis in patients that would go on to develop CTEPH [10]. Although current ESC guidelines recommend against routine screening for CTEPH post-PE [3], certain populations at elevated risk may benefit from being followed more closely, including those with pulmonary hypertension already present at the time of PE diagnosis [11].

The authors believe that combining the use of functional indices of the RV (acceleration time, RV outflow tract doppler envelope, and the presence of septal dyskinesia, to name a few), with invasive monitoring to detect improvements in PAP, is a potential approach to reaching physiologically meaningful goals while limiting the risks associated with thrombolytics. These risks are well-documented, and can include hemodynamically significant and life-threatening intra- and extracranial bleeding, as documented in the PEITHO trial [12]. The MOPETT trial demonstrated that the optimal lytic dose has not yet been determined, and that a lower dose (half of that typically used) was efficacious with less adverse effects in a group with high-risk PE [2]. Zhang et al.'s

meta-analysis likewise suggests that a lower thrombolytic dose may be associated with less hemorrhagic complications [13]. Several other studies looking at catheter-directed therapy (the ULTIMA, SEATTLE2 and PERFECT trials) showcased how more invasive approaches including thrombolysis can improve mortality in submassive populations [14–16]. In the PERFECT trial, where the average total dose used was 28 mg, there were no significant hemorrhagic complications [16].

Given these data, it would be logical to try to find the lowest effective dose to maximize patient safety. In this case, we feel that significant physiological and clinical improvement was achieved with a significantly lower dose of thrombolysis (about 30% of a typical amount). In our opinion, POCUS likewise plays a central role in screening for and assessing the degree of RV dysfunction and contributes to the decision to potentially escalate therapy. While a PA catheter is not strictly needed, with experienced nursing and adequate resources it provides reliable PA pressure monitoring, which we feel should be the main parameter to follow as it is the root cause of the hemodynamic disturbance. Alternately, frequent POCUS assessments of several parameters could also replace the use of a PA catheter for an entirely non-invasive method. This approach, whether PA catheter-based or not, is fairly simple and can also be done in any intensive care unit; it is not limited to centers with advanced interventional radiology capabilities.

CONCLUSION

The optimal management of patients presenting with intermediate-risk acute PE is an area that has tremendous potential for research and improvement in management, given the broad physiological spectrum of the disease and ongoing significant morbidity and mortality with standard conservative management. Given the ongoing advances in management of PE, we believe that more attention should be focused on risk stratification and therapeutic strategies. Trials that do not assess RV functionality, particularly V-A coupling, while easier to perform on a large scale, will inherently be unable to properly identify the patients who may most benefit from a more aggressive therapy. We truly hope that academic centers with sufficient means can devise a multi-arm trial with physiological assessment paired with the different available strategies, invasive and non-invasive, to guide clinicians through the large gray zone that exists within acute PE.

Ethics Statement

(1) All the authors mentioned in the manuscript have agreed to authorship, read and approved the manuscript, and given consent for submission and subsequent publication of the manuscript.

(2) The authors declare that they have read and abided by the JEVTM statement of ethical standards including rules of informed consent and ethical committee approval as stated in the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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