Role of Pulmonary Embolism Response Team in patients with intermediate- and high-risk pulmonary embolism: a concise review and preliminary experience from China

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Abstract

Intermediate- and high-risk pulmonary embolism (PE) is a life-threatening medical emergency with high morbidity and mortality. Many of the treatment options for PE involve clinicians from multiple disciplines. Pulmonary Embolism Response Teams (PERTs) have been developed to coordinate the multidisciplinary team of clinicians to streamline the decision making process and develop individualised treatment plans in a timely fashion. The first PERT was established in 2012 and subsequently multiple centres worldwide have introduced this model for the management of intermediate- and high-risk PE. In this review, we evaluate the organisational structure and algorithms of different PERT services and compare data from pre- and post-PERT services to determine the impact of PERT on outcomes. We consider the cost and time implications of this multidisciplinary 24-hour service and suggest areas for further research and review.

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1 Introduction

Pulmonary embolism (PE) is a complex condition that is easily missed or misdiagnosed. With a range of clinical manifestations, the diagnosis, treatment and management of PE can be challenging. In the United States, 240,000 cases of non-fatal PE are diagnosed each year and there are 300,000 deaths from acute PE annually.[1,2] It is reported that the mortality due to untreated PE is as high as 25%–50%.[3,4] Currently, the PE is the third leading cause of death, following myocardial infarction and stroke.[5,6] Due to the nonspecific presentation of PE: shortness of breath, chest pain, palpitations; and hypoxia: many patients with acute PE are misdiagnosed.[7] Therefore, it is likely that the mortality rates of PE are underestimated and underreported.[8]

The clinical manifestation of PE is varied and can range from an asymptomatic onset to hemodynamic collapse. Just like any other high-risk cardiovascular events, the European Society of Cardiology (ESC) have developed guidelines that focus on risk stratification and appropriate treatment (Table 1). Different risk stratification of PE has different early mortality and therapeutic decisions.[9,10] A wide range of treatment methods are established to manage intermediate- and high-risk PE, including non-vitamin K-dependent oral anticoagulant, systemic thrombolysis, catheter-directed treatment (CDT), catheter embolectomy, inferior vena cava filters, surgical embolectomy, and extracorporeal membrane oxygenation.[9,11–28] The best treatment choice for the patient can vary greatly between individual cases, making standardized care difficult.[21,22] The management options for this potentially fatal disease span multiple specialties,[11,23,24] and some treatments remain controversial.[25–28] Therefore, multiple experts from different fields are required acutely to determine the best treatment plan for the individual affected by acute PE, requiring considerable co-ordination. In order to address the needs of modern systems-based healthcare, multidisciplinary Pulmonary Embolism Response Teams (PERTs) have been developed.[9,29–35] In this review, we summarize the establishment, development and activation process of PERT. We discuss the benefits and challenges of PERT operation and consider areas for further research.
Table 1. Risk stratification and definitions of acute PE based on the European Society of Cardiology guidelines.

| Risk stratification of acute PE | Definitions |
|--------------------------------|-------------|
| High-risk PE                  | Persistent hypotension or Obstructive shock or Cardiac arrest |
| Intermediate-risk PE          | sPESI Score 1 or more |
| Intermediate-high-risk PE     | Right ventricular dysfunction or Biomarker elevation: both positive |
| Intermediate-low-risk PE      | sPESI Score 1 or more |
| Low-risk PE                   | Right ventricular dysfunction or Biomarker elevation: either one positive |
|                               | Hemodynamically stable and no right ventricular dysfunction or Biomarker elevation |

Persistent hypotension refers to systolic BP < 90 mmHg or systolic BP drop ≥ 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolaemia, or sepsis. Obstructive shock refers to systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥ 90 mmHg despite adequate filling status and end-organ hypoperfusion (altered mental status, cold, clammy skin, oliguria/anuria; increased serum lactate). Cardiac arrest refers to need for cardiopulmonary resuscitation. Biomarker elevation refers to BNP/troponin. BP: blood pressure; PE: pulmonary embolism; sPESI: simplified pulmonary embolism severity index.

2 Current development of PERT

In order to improve the treatment efficiency and management of patients with intermediate- and high-risk PE, the Massachusetts General Hospital (MGH) set up the world’s first PERT in 2012. The PERT integrates specialists in cardiology, emergency medicine, pulmonary medicine, critical care and intervention. These experts constitute a highly specialist multidisciplinary team offering treatment advice to the patients with intermediate- and high-risk PE. Subsequently, many other medical institutions in the United States have established PERT.

Following success with PERT in the United States, multiple other centres have developed PERT internationally.

On July 5 2017, Beijing Anzhen Hospital (affiliated to Capital Medical University) integrated ten departments and established China’s first multidisciplinary team to provide timely diagnosis and effective treatment for patients with PE. The team spans multiple departments: emergency medicine, respiratory, pulmonary critical care, interventional cardiology, vascular medicine, cardiothoracic surgery, hematology, radiology, echocardiography and nuclear medicine (Figure 1). The PERT structure is divided into five working groups according to the clinical needs, these include protocol development, clinical practice, education, research and communication group (Figure 2); the five groups are coordinated by the secretariat office and have corresponding responsibilities (Figure 3). They share information through the convenient online consultation (WeChat platform) with the purpose of rapid response, joint action and right decision-making for critically ill patients with PE.

The PERT composition varies greatly from country to country, and generally consists of 3–10 departments. According to different medical institutions, the core departments often include cardiology, cardiothoracic surgery, pulmonary & critical care, interventional radiology and emergency medicine (Table 2).

Figure 1. PERT in Beijing Anzhen Hospital. PERT: pulmonary embolism response team.

Figure 2. PERT structure in Beijing Anzhen Hospital. PERT: pulmonary embolism response team.

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Figure 3. **PERT Working Group responsibilities in Beijing Anzhen Hospital.** PE: pulmonary embolism; PERT: pulmonary embolism response team.

Table 2. **Summary of characteristics of PERT model in different countries.**

| Author       | Country | Year | Department number | Department composition                                                                 | Activate way       | Stratification of PE                  |
|--------------|---------|------|-------------------|----------------------------------------------------------------------------------------|--------------------|---------------------------------------|
| Serhal, et al.[11] | USA     | 2014 | 9                 | Vascular medicine, pulmonary and critical care medicine, interventional and general cardiology, interventional and diagnostic radiology, cardiothoracic surgery, hematology, internal medicine, pharmacists, emergency room physicians | Skype              | Intermediate-risk PE                  |
| Merli, et al.[31] | USA     | N/A  | 4                 | Interventionalist, critical care pulmonologist, radiologist, vascular medicine specialist | N/A                | High-risk PE or Intermediate-high-risk PE |
| Rosovsky, et al.[33] | USA     | 2012 | 10                | Vascular medicine, pulmonary and critical care, interventional and general cardiology, interventional radiology, cardiac surgery, ultrasound, hematology, pharmacists, emergency room, vascular surgery Cardiology, vascular surgery, pulmonary and critical care, hematology, emergency medicine, interventional radiology, hospital medicine, cardiac surgery, nursing, pharmacy | Telephone call     | High-risk or Intermediate-risk PE     |
| Xenos, et al.[34]   | UK      | 2015 | 10                | Emergency medicine, respiratory, pulmonary critical care, interventional cardiology, vascular medicine, cardiothoracic surgery, hematology, radiology, echocardiography, nuclear medicine | Telephone call     | High-risk or Intermediate-risk PE     |
| NIE, et al.[38]     | China   | 2017 | 10                | Cardiology, cardiothoracic surgery, critical care medicine | Online platform (WeChat) | High-risk or Intermediate-risk PE |
| Jen, et al.[39]     | Singapore | 2015 | 3 core faculty    | Cardiology, cardiothoracic surgery, critical care medicine | Telephone call     | High-risk or Intermediate-risk PE     |
| Galmer, et al.[43]  | USA     | N/A  | N/A               | N/A                                                                                     | Telephone call     | High-risk or Intermediate-risk PE     |
| Araszkiewicz, et al.[46] | Poland   | 2019 | 2 groups (7+6)    | The first group (permanent PERT team): intensive cardiac therapy, echocardiography, interventional cardiology, cardiac surgeons, emergency medicine, anesthesiologists and radiologists (interventional radiologists) The second group (if necessary): neurologists, neurosurgeons, oncologists, vascular surgeons, hematologists and specialists in lung disease | Telephone call     | Intermediate-high-risk PE             |

N/A: not applicable; PE: pulmonary embolism; PERT: pulmonary embolism response team.

3 **PERT Consortium**

In 2015, the international PERT Consortium was established to promote the multidisciplinary team treatment concept, providing rapid and individualized diagnosis and treatment for complicated patients with acute PE.[22,40] The
international PERT Consortium has grown steadily in just a few years.[21,37,41]

The China’s Consortium of PERTs has promoted the multidisciplinary treatment model for PE and is accepted as a full member of the international PERT alliance. It has the following aims: (1) promote concept of PE care and create exchange platform; (2) introduce and generalize technique and train teams of PE care; (3) set up teams of PE care and improve standard algorithm; (4) conduct clinical study to compile the database; (5) enhance international collaboration to promote integration; and (6) conduct device development to improve innovation and translation.[38]

Significant medical resources are required to develop a PERT,[32] therefore, not all hospitals have the infrastructure to support this. Individual hospitals should develop PERT in accordance with local resource availability across equipment, personnel and funding. As a result, there remains some inter-hospital variation in PERT structure.[11,33,34,42–44]

4 Activation process of PERT

The PERT is activated in the MGH when a patient is suspected or confirmed to have an intermediate- or high-risk PE. Vascular medicine and interventional radiology fellows are the backbones of PERT.[23,36] The fellows’ initial role is to confirm the diagnosis of PE and risk stratify, deciding the appropriateness of activating PERT. For patients with low-risk PE, it is generally unnecessary to activate PERT and appropriate anticoagulation can be commenced. However, most intermediate- and high-risk PE cases are presented to the PERT and the primary clinical PERT members are invited to participate in the discussion. The PERT aims to form a consensus-based treatment plan following the review of online medical records and pertinent imaging, such as computed tomography pulmonary angiogram (CTPA), electrocardiogram (ECG), echocardiography images and laboratory reports.[29] The PERT will then triage the patient to the appropriate department. The patients are followed up by PERT fellows during their hospital admission and after discharge (Figure 4).[23]

At the Cleveland Clinic, patients with PE are often diagnosed by VQ or CTPA imaging. The clinical data including history, physical examination, cardiac biomarkers (BNP or NT-pro BNP and troponin), echocardiography, ECG, CTPA and other relevant investigations are collected by a designated fellow for risk stratification of patients with PE. If the patient is identified to have an intermediate-risk PE: according to right ventricular strain and elevated biomarkers, the PERT members are informed and a discussion launched via Skype. The PERT consultation specialists will review

Figure 4. Activation flowchart of MGH’s PERT. CTPA: computed tomography pulmonary angiogram; ECG: electrocardiogram; HIPAA: Health Insurance Portability and Accountability Act; ICU: intensive care unit; MGH: Massachusetts General Hospital; PE: pulmonary embolism; PERT: pulmonary embolism response team.

the patient’s details, assess the bleeding risk, and weigh up the risks and benefits of intervention or surgery. The agreed treatment plan will then be commenced, this process generally takes less than 90 min. The PERT team is responsible for notifying the appropriate department to commence the treatment plan. Patients are followed up by the vascular medicine team during hospitalization or following discharge. If the patient is haemodynamically stable, with no evidence of right ventricular strain or elevated biomarkers, a low risk PE is diagnosed. Therefore, anticoagulant therapy will be commenced without the requirement for further intervention. If the patient develops haemodynamic compromise or shock, this is classified as high-risk PE. Therefore, systemic thrombolysis or thrombectomy will be pursued according to guidelines. The figure summarizes the process of the Cleveland Clinic PERT when intermediate-risk PE is diagnosed (Figure 5).[11]

At Beijing Anzhen Hospital (affiliated to Capital Medical University), the PERT on-call physician is notified when a suspected or diagnosed PE is identified and the PERT is activated by the doctor. All patients with PE undergo a comprehensive assessment and risk stratification to screen for intermediate- and high-risk PE. If the patient has a low-risk PE, then he/she will be commenced on anticoagulation and followed-up after discharge. However, if the patient suffers from intermediate- or high-risk PE, the physician of
Figure 5. Activation flowchart of the Cleveland Clinic’s PERT. CTPA: computed tomography pulmonary angiogram; PE: pulmonary embolism; PERT: pulmonary embolism response team; RV: right ventricle; VQ: ventilation-perfusion.

PERT will send the patient’s relevant medical records (including blood results, imaging, ECG and echocardiography) to the wider PERT through the WeChat platform. The experts will review the medical records and weigh up the risks and benefits of further intervention on an individual case basis. Once the optimum treatment plan is decided upon this will be discussed with patient and family, and the patient will be transferred to the appropriate ward for treatment [usually intensive care unit (ICU)]. All patients are followed up in PERT clinic after discharge (Figure 6).[38]

Not all patients with PE need to activate PERT. Therefore, the patients who need to initiate PERT are mostly intermediate- or high-risk PE ones, and a few are low-risk PE patients with complicated conditions. The activation modes of PERT in different countries are summarized (Table 2).

5 Clinical outcomes and implications after PERT administration

After the establishment of the first PERT in the MGH, the PERT has emerged around the world. This new multidisciplinary treatment model was demonstrated through different researches. During the past years, both of the positive and optimistic results were obtained through PERT.

Bloomer, et al.[45] established an acute PE network and transferred all patients with acute PE via PERT through this network. A total of 31 patients (including 14 patients from the acute PE network and 17 patients from the emergency department) with intermediate-risk PE were treated with ultrasound-assisted CDT via PERT. Echocardiography was performed before and after ultrasound-assisted CDT treatment of the patients. Right ventricular function in 94% of patients was improved or preserved, and right ventricular size in 88% of patients was improved or preserved. The data showed that the development of an acute PE network alongside PERT was an effective critical care pathway for ultrasound-assisted CDT treatment of patients with intermediate-to high-risk PE. They identified the PERT as a valuable medical decision-making resource, improving efficiency, especially in the treatment of high-risk PE.[46]

Xenos, et al.[34] report large reductions in length of ICU stay and overall length of stay in hospital for patients managed with PERT when compared with the control group. Notably, there was no significant difference in healthcare costs for patients treated via PERT despite more frequent use of higher cost interventional treatments. There was no difference in mortality rate between the PERT and control groups.[34,37,47]

The management of intermediate- and high-risk PE remains challenging. Mahar, et al.[48] retrospectively analyzed all patients admitted to the Cleveland Clinic main campus between 2014 and 2016, there were 134 PERT activations, patients were classified into low-, intermediate- or high-risk PE. The 68% of patients were classified as intermediate-risk PEs and 19% of patients were classified as high-risk PEs. Within this cohort of 134 patients, 12% of patients underwent CDT with recombinant tissue plasminogen activator (rt-PA), 5% of patients received full dose (rt-PA: 100 mg), 13% of patients were treated with systemic half-dose (rt-PA: 50 mg), 5% of patients underwent surgical embolectomy and 3% of patients mechanical thrombectomy. The 55% of
patients received anticoagulation as monotherapy, whilst 7% of patients were managed conservatively. A 9% in-hospital mortality was reported. Following the introduction of PERT at the Cleveland Clinic, they report significant improvement in PE management across a number of domains: fewer bleeding events, quicker initiation of therapeutic anticoagulation and a significant reduction in 30 day mortality. These differences were most marked in patients with intermediate- and high-risk PEs.\[49\]

Brailovsky, et al.\[50\] conducted a survey of hospital staff to assess understanding of PERT. They also assessed the impact of PERT education sessions on clinicians’ ability of risk stratify and manage acute PE. Results showed an improvement in clinicians’ ability of risk stratify PE (60.2% to 73.8%) and an increased awareness of the role of the PERT (72.2% to 92.6%). Overall, a higher proportion of surveyed clinicians stated they feel comfortable managing acute PE following this focused education session (improvement from 82% to 90%). This study demonstrates the benefits of PERT education in improving overall confidence and skill in managing acute PE.

Elbadawi, et al.\[51\] published a similar study focusing on the educational benefits of PERT for the wider clinical team. They identified improved skill and confidence of managing acute PE, when reviewed one year after the implementation of PERT. Surveyed participants self-reported an improved understanding of the pathophysiology and management of high-risk PE. The 89% of respondents felt that PERT improved the care of patients with PE in that institution.\[57\]

Wright, et al.\[52\] compared the treatment modalities used for patients with intermediate- or high-risk PE prior to and following PERT introduction. Prior to PERT, the 85% of patients received heparin and 15% of patients received advanced treatment. Following the introduction of PERT, the 68% of patients received heparin alone and 32% of patients received advanced treatments. This significant change suggests patients are treated more aggressively following the introduction of PERT. They report an improved efficiency in the management of PE, the time from triage to diagnosis in the emergency department (ED) was significantly reduced (384 vs. 212 min, 45% lower, \( P < 0.05 \)), and the time from diagnosis to heparin administration was also decreased (182 vs. 76 min, 58% lower, \( P < 0.05 \)). This demonstrates that patients with PE received more aggressive and advanced treatments, and significantly accelerated care in the ED after the implementation of PERT.\[52\]

It is also important to consider the challenges with implementing PERT. Schultz, et al.\[53\] conducted the first multicenter study of PERT across eight medical centers in the United States. The data report 475 activations in the PERT Consortium, of which 88% of the patients were diagnosed with acute PE. The number of PERT activations varied between medical centers. The 59.3% of PERT activations originated from the emergency department. Of the 475 cases, 69% of patients were stratified as intermediate-risk, 12% of patients as high-risk, and 19% of patients as low-risk. Anticoagulation alone was the most common treatment: received by 70% of patients. The proportion of patients receiving other advanced therapies varied largely between institutions, ranging from 16% to 46%. The 30-day mortality ranged significantly from 9% to 44%. These results demonstrate the large variability in PE severity, treatment received and mortality between centres within the PERT Consortium. Further studies from other medical centres are needed to confirm the improvement in 30-day mortality with the introduction of PERT.

In a number of medical centers, the PERT is only activated in response to intermediate- and high-risk PE, and not for low-risk PE. Sista, et al.\[47\] conducted a retrospective analysis of PERT’s 20-month data and found that the electronic medical records were incomplete. The number of activations was sparse during the first ten months of PERT operation. This research only focused on patients with intermediate- and high-risk PE, and did not assess the patients with low-risk PE, affecting the generalizability of these results.

Deadmon, et al.\[54\] studied the impact of patient location at the time of PERT activation on treatment decisions, time to treatment and outcome. The patients were divided into three groups according to the source of PERT activation: ED, ICU, or non-ICU inpatient ward. The number of PERT activations occurring during the day, night or weekend; and the percentage of PE, severity of disease, treatment and outcome were compared. The results showed that the location of PE activation impacted management decisions and outcomes for patients. They highlight the importance of tailoring the PERT service to the individual clinical area.

Alongside the benefits of PERT, it is important to consider the cost burden of running a 24-hour multidisciplinary team.\[37\] Nouri, et al.\[55\] designed a study to determine whether PERT improves patient outcomes within their centre. They stratified patients into intermediate- and high-risk PE cohorts through using cardiac biomarkers, echocardiography and hemodynamic status. The participants were then divided into two groups: pre-PERT and early-PERT. The overall mortality in hospital was 11.8%. In-hospital mortality of pre-PERT and early-PERT are 14.6% and 8.8% (\( P = 0.15 \)), respectively. Moderate-to-severe bleeding events were reported at a frequency of 17.7% of pre-PERT and 10.4% of early-PERT (\( P = 0.095 \)). The results of the sin-
The integration of multidisciplinary experts with differing clinical backgrounds, familiarities with different techniques and technologies remains one of the challenges with PERT. Our review of the literature has identified a number of steps within the PERT pathway that would benefit from further study including: the optimum time to activate PERT, the follow-up of PERT patients, the impact of PERT on quality of life/longer term symptomatic burden, and the education and training of PERT team members. Increased initiation of PERT will in turn increase financial cost and time burden for involved staff. In the most PERTs, clinicians are on standby 24 hours a day, which is an important consideration for work scheduling. Additionally, the most PERT experts are currently offering time freely to their teams, so the financial implications for on call time must be considered when assessing the viability of PERT and the criteria for initiating PERT.

7 Conclusions

The assessment, treatment and management of patients with intermediate- and high-risk PE remains variable within and between medical centres. Given the spectrum of severity of PE and wide range of treatment options, there is currently no standardized treatment guideline. The PERT presents a new concept to aid timely decision making, utilizing the skills of the multidisciplinary PERT, to form an individualized treatment plan. Our review of the literature demonstrates good initial outcomes with PERT, especially regarding efficiency of treatment initiation, staff education and training and the use of more invasive procedures. A clear mortality benefit is yet to be demonstrated. Further studies are required to determine the longer-term benefits of PERT and to evaluate the cost-effectiveness of this resource intensive multidisciplinary decision-making tool.

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