Impact of Multidisciplinary Pulmonary Embolism Response Team Availability on Management and Outcomes

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Treatment strategies for complex patients with pulmonary embolism (PE) are often debated given patient heterogeneity, multitude of available treatment modalities, and lack of consensus guidelines. Although multidisciplinary Pulmonary Embolism Response Teams (PERT) are emerging to address this lack of consensus, their impact on patient outcomes is not entirely clear. This analysis was conducted to compare outcomes of all patients with PE before and after PERT availability. We analyzed all adult patients admitted with acute PE diagnosed on computed tomography scans in the 18 months before and after the institution of PERT at a large tertiary care hospital. Among 769 consecutive inpatients with PE, PERT era patients had lower rates of major or clinically relevant nonmajor bleeding (17.0% vs 8.3%, p = 0.002), shorter time-to-therapeutic anticoagulation (16.3 hour vs 12.6 hour, p = 0.009) and decreased use of inferior vena cava filters (22.2% vs 16.4%, p = 0.004). There was an increase in the use of thrombolytics/catheter-based strategies, however, this did not achieve statistical significance (p = 0.07). There was a significant decrease in 30-day/inpatient mortality (8.5% vs 4.7%, p = 0.03). These differences in outcomes were more pronounced in intermediate and high-risk patients (mortality 10.0% vs 5.3%, p = 0.02). The availability of multidisciplinary PERT was associated with improved outcomes including 30-day mortality. Patients with higher severity of PE seemed to derive most benefit from PERT availability. **(Am J Cardiol 2019;124:1465−1469)**

It is estimated that about 200,000 to 400,000 patients are diagnosed with acute pulmonary embolism (PE) in the United States annually.[1,2] Management of acute PE is primarily guided by disease severity. Whereas systemic fibrinolytics for massive PE patients is rarely debated[3]; the most appropriate strategy for other large patient-groups such as intermediate-risk PE is debated frequently.[4] This is reflected by the lack of consensus between various society guidelines on PE.[5-7] Given this lack of consensus, patient heterogeneity and availability of various treatment modalities - a multidisciplinary approach to management is being widely adopted. The Pulmonary Embolism Response Team (PERT) was first described in 2013, to aid in rapid risk-stratification along with development and execution of a management strategy.[8,9] Despite the emergence of PERTs there is paucity in literature regarding the impact of PERT availability.[10-15] Here, we studied how the availability of PERT affected patient management and outcomes.

Methods

The PERT program at Cleveland Clinic (CC) was launched in July 2014. The composition of PERT and the activation process have been described previously.[11] In this study, we performed a retrospective cohort analysis of all adult patients (>18 years), diagnosed with acute PE by Computed Tomography-PE protocol (CT-PE) at CC, who received care in the emergency room or inpatient wards between January 1, 2013 and June 30, 2014 (pre-PERT era) and January 1, 2015 and June 30, 2016 (PERT era). Data from July 1, 2014 to December 30, 2014 were not analyzed and deemed as a "run-in" period allowing for the dissemination of information regarding PERT availability hospital-wide. The duration for the "run-in" period was determined as the number of PERT activations/month at our hospital initially increased and then plateaued starting January 2015 (data not shown). All patients diagnosed with an acute PE were screened from the CC radiology CT database. Patients with PE limited to the subsegmental pulmonary arteries were excluded. Patients who received only out-patient care or care at a satellite CC campus were not included in the study as PERT was not available to these patients. For patients with multiple positive CTs in the study period, only the first hospitalization was used for this analysis. All patients with acute PE, irrespective of their PERT

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activation status, were included in the study. The Institutional Review Board at CC approved the study.

Patient charts were individually reviewed to gather several variables including age, gender and vital signs at the time of the CT scan. Other Pulmonary Embolism Severity Index (PESI) variables including history of malignancy, heart failure, or lung disease were also noted. Presence of RV dysfunction was noted if it was documented on the echocardiogram report. Elevated brain natriuretic peptide (BNP) (ADVIA Centaur BNP >100 pg/mL, Bayer Diagnostics, Tarrytown, NJ), cardiac troponin T and NT-ProBNP (Elecsys 4th Gen TnT >0.01 ng/mL, proBNP II >300 pg/mL Roche Diagnostics USA, Indianapolis, IN) and was noted. Any venous duplex studies positive for acute deep vein thrombosis (DVT) were also noted.

The management strategies implemented were classified as supportive care (no anticoagulation) or standard management (anticoagulation). In the standard management group, use of advanced strategies including systemic (full vs half dose) or catheter-directed thrombolysis, aspiration thrombectomy, surgical embolectomy, venoarterial extracorporeal membrane oxygenation (ECMO) use was noted. The use of IVC filters was noted separately from the other advanced strategies. For standard management patients, the time-to-therapeutic anticoagulation was noted. This was defined as time between the acquisition of the CT scan to achieving the first therapeutic/supratherapeutic aPTT (heparin or bivalirudin), or to peak effect of oral/injectable drug after administration per respective package insert (Enoxaparin − 4 hour Sanofi US, Bridgewater, NJ; Rivaroxaban - 3 hours Janssen Pharmaceutical, Titusville, NJ and Fondaparinux − 3hr Glaxosmithkline, Philadelphia, PA). All major and clinically relevant nonmajor (CRNM) bleeding events, as defined by the International Society of Thrombosis and Hemostasis (ISTH), were noted.[16] The proportion of patients with bleeding was represented as a percentage of all standard management patients.

Patient characteristics and PE severity were compared for the entire pre-PERT and PERT era cohorts. Further, prespecified analysis was conducted specifically for intermediate- and high-risk patients (ESC definition[5]). This cohort included all patients with any of the following features: hypotension, simplified PESI score ≥1, PESI score III-V, positive cardiac biomarkers or RV dysfunction. The primary outcome variable was prespecified as all-cause 30-day mortality and mortality during the index hospital admission (if admission >30 days). Secondary prespecified measures included management strategies adopted, IVC filter placement, time-to-therapeutic anticoagulation, and bleeding events. All categorical and continuous variables were compared using Chi-Square test and student's *t* test respectively. Significance was assessed using two-tailed p value <0.05. All analysis was done using IBM-SPSS (Version 25) software.

Results

A total of 769 unique patients were identified to satisfy the study inclusion criteria. As shown in Table 1A, no significant differences were noted between the pre-PERT and

Table 1
Baseline characteristics of PE patients in the pre-PERT and PERT eras

Variable	Pre-PERT	PERT	p Value
(A) Entire cohort			
Number of patients	343	426	
Age (years)	58.1 ± 14.9	57.2 ± 16.2	0.392
Males	174 (50.7%)	222 (52.1%)	0.703
Cancer	113 (32.9%)	136 (31.9%)	0.764
Cardiopulmonary disease	139 (40.5%)	213 (50.0%)	0.009*
Positive cardiac biomarkers	117 (34.1%)	185 (43.4%)	0.009*
Right ventricular dysfunction	77 (22.4%)	123 (28.9%)	0.044*
Positive deep vein thrombosis	151 (44.0%)	199 (46.7%)	0.456
Simplified pulmonary embolism severity index	1.7 ± 1.3	1.9 ± 1.2	0.010*
Pulmonary embolism severity index	105.2 ± 38.8	111.4 ± 44.4	0.042*
Pulmonary embolism response team activations	-	57 (12.5%)	
Variable	Pre-PERT	PERT	p Value
(B) Intermediate/high-risk patients			
Number of patients	289	378	
Age (years)	59.5 ± 14.3	58.4 ± 15.9	0.339
Males	146 (50.5%)	203 (53.7%)	0.414
Active cancer	113 (39.1%)	136 (36.0%)	0.409
Cardiopulmonary disease	139 (48.1%)	213 (56.3%)	0.034*
Positive cardiac biomarkers	117 (40.5%)	185 (48.9%)	0.030*
Right ventricular dysfunction	77 (26.6%)	123 (32.5%)	0.100
Positive deep vein thrombosis	131 (45.3%)	176 (46.6%)	0.752
Simplified pulmonary embolism severity index	2.0 ± 1.1	2.2 ± 1.1	0.060
Pulmonary embolism severity index	113.8 ± 35.1	118.7 ± 41.4	0.102
Pulmonary embolism response team activations	-	55 (14.6%)	

PE=− pulmonary embolism, PERT = Pulmonary Embolism Response Team.
* Denotes statistical significance.

Table 2
Management strategies adopted and outcomes in the pre-PERT and PERT eras

Variable	Pre-PERT (n = 343)	PERT (n = 426)	p Value
(A) Entire cohort			
Supportive care/no anticoagulation	25 (7.3%)	18 (4.2%)	0.082
Standard management	318 (92.7%)	408 (95.8%)	0.082
Anticoagulation alone	309 (97.2%)	385 (94.4%)	0.071
Advanced strategies	9 (2.8%)	23 (5.6%)	0.071
Time to therapeutic anticoagulation (hours)	16.3 ± 23.3	12.6 ± 14.9	0.009*
First anticoagulant used			
Heparin	264 (83.0%)	356 (87.2%)	0.113
Enoxaparin	50 (15.7%)	49 (12.0%)	0.232
Bivalirudin	3 (0.9%)	2 (0.5%)	0.658
Fondaparinux	1 (0.3%)	2 (0.5%)	1.000
Rivaroxaban	0 (0%)	1 (0.2%)	1.000
Inferior vena cava filter	76 (22.2%)	70 (16.4%)	0.004*
Major + Clinically relevant nonmajor bleeding	54/318 (17.0%)	34/408 (8.3%)	0.002*
Mortality (30-day or inpatient)	29 (8.5%)	20 (4.7%)	0.034*
Variable	Pre-PERT (n = 289)	PERT (n = 378)	p Value
(B) Intermediate/high-risk patients			
Supportive care/no anticoagulation	24 (8.3%)	17 (4.5%)	0.051
Standard management	265 (91.7%)	361 (95.5%)	0.051
Anticoagulation alone	256 (96.6%)	338 (93.6%)	0.102
Advanced strategies	9 (3.4%)	23 (6.4%)	0.102
Time to therapeutic anticoagulation (hours)	16.8 ± 24.5	13.2 ± 15.7	0.025*
First anticoagulant used			
Heparin	220 (83.0%)	315 (87.3%)	0.168
Enoxaparin	42 (15.8%)	41 (11.4%)	0.121
Bivalirudin	2 (0.8%)	2 (0.6%)	1.000
Fondaparinux	1 (0.4%)	2 (0.6%)	1.000
Rivaroxaban	0 (0%)	1 (0.3%)	1.000
Inferior vena cava filter	71 (24.6%)	61 (16.1%)	0.008*
Major + Clinically relevant non-major bleeding	51/265 (19.2%)	31/361 (8.6%)	<0.001*
Mortality (30-day or inpatient)	29 (10.0%)	20 (5.3%)	0.020*

PE = Pulmonary Embolism, PERT = Pulmonary Embolism Response Team.
* Denotes statistical significance.

PERT era patients when comparing average age, gender, malignancy or concomitant DVT diagnosis. In the PERT era, more patients had existing cardiopulmonary disease (40.5% vs 50%; p = 0.009), elevated cardiac biomarkers (34.1% vs 43.4%; p = 0.009), and RV dysfunction (22.4% vs 28.9%; p = 0.044) when compared with the pre-PERT era. The calculated PESI and sPESI scores were also statistically higher in the PERT-era (105.2 vs 111.4; p = 0.042 and 1.7 vs 1.9; p = 0.010) compared with pre-PERT patients. The PE response team was involved in the care of 57 patients (12.5% of all PERT era patients). Echocardiograms were unavailable in 20.7% of pre-PERT and 20.2% of PERT era patients (p = 0.86). Cardiac biomarkers were unavailable in 25.1% of pre-PERT and 14.3% of PERT era patients (p <0.05). In the intermediate- and high-risk group, there was no significant difference in average age, gender, history of malignancy, DVT or RV dysfunction between the pre-PERT and PERT eras (p >0.3 for all). There were a statistically higher number of patients with cardiopulmonary disease (48.1% vs 56.3%; p = 0.034) and positive cardiac biomarkers (40.5% vs 48.9%; p = 0.03) in PERT era compared with the pre-PERT era. Calculated PESI and sPESI scores were not statistically different in the pre-PERT and PERT groups. About 15% of patients (n = 55) in the PERT era group had PERT involvement.

As shown in Table 2A, <8% patients were managed without any anticoagulation in the study cohort. Of the patients managed with some form of standard management, >94% of patients were managed with anticoagulation alone. There was no statistical difference in the proportion of patients receiving advanced strategies (p = 0.071). Further categorization of these advanced therapies is provided in the supplemental data (S1). The type of anticoagulant used was similar in the two groups. A significant decrease in the use of IVC filters in the PERT-era versus pre-PERT cohort was noted (22.2% vs 16.4%; p = 0.004). The primary outcome of all-cause 30-day/index hospital admission mortality was significantly lower in the PERT-era compared with pre-PERT patients (8.5% vs 4.7%; p = 0.034). Time-to-therapeutic anticoagulation was also shorter in the PERT era (16.3 hour vs 12.6 hour; p = 0.02). Finally, the composite of all major and CRNM bleeding was significantly higher in the pre-PERT era (17.0% vs 8.5%).

As was true for the entire cohort, the proportion of intermediate- and high-risk patients treated with various management strategies were not statistically different in the pre-PERT and PERT eras (Table 2B). Further, anticoagulation strategy was also not statistically different in the two groups. However, significantly fewer IVC filters were placed in the PERT era (24.6% vs 16.1%; p = 0.008). There

Table 3
Baseline characteristics and management strategies/outcomes of patients with active involvement of PERT

Variable	PERT activations (n = 57)
Baseline characteristics	
Age (years)	56.5 ± 16.7
Males	32 (56.1%)
Cancer	14 (24.6%)
Cardiopulmonary disease	31 (54.4%)
Positive cardiac biomarkers	48 (84.2%)
Right ventricular dysfunction	40 (70.2%)
Positive deep vein thrombosis	38 (66.7%)
Simplified pulmonary embolism severity index	2.5 ± 1.2
Pulmonary embolism severity index	131.9 ± 48.0
Management/Outcomes	
Supportive care/no anticoagulation	0 (0.0%)
Standard management	57 (100%)
Anticoagulation alone	41 (71.9%)
Advanced strategies	16 (28.1%)
First anticoagulant used	
Heparin	56 (98.2%)
Enoxaparin	1 (1.8%)
Time to therapeutic anticoagulation (hours)	11.6 ± 15.1
Inferior vena cava filter	17 (29.8%)
Major + Clinically relevant non-major bleeding	10 (17.5%)
Mortality (30-day or inpatient)	2 (3.5%)

PERT = Pulmonary Embolism Response Team

was a higher 30-day/index admission mortality in pre-PERT compared with PERT era (10% vs 5.3%; p = 0.020). There was significantly less major and/or CRNM bleeding (19.2% vs 8.6%; p = 0.001) and shorter time-to-therapeutic anticoagulation (16.8 hour vs 13.2 hour; p = 0.043) in the PERT era. Table 3 summarizes baseline characteristics, management and outcomes of all patients that had direct involvement of the PERT team in their hospital care.

Discussion

The impact of PERTs on patient outcomes remains elusive, despite the gradual emergence of such teams in the last few years. To our knowledge, this is the first study to compare outcomes of all PE patients before and after the availability of a PERT. In this analysis, PERT availability was associated with decreased 30-day/inpatient mortality, decreased bleeding and shorter time-to-therapeutic anticoagulation. There was a trend toward increase in the use of catheter-directed and systemic thrombolysis in the PERT era, however, this did not achieve statistical significance. Moreover, there was a decrease in IVC filter use. Finally, when advanced strategies were adopted − it was done with the guidance of the multidisciplinary team.

There are previously published individual institution data describing treatment strategies and patient outcomes after PERT.[10-14] Recently, Rosovsky et al also compared management strategies and outcomes of ED patients managed by their PERT team to a historical cohort at their institution.[17] Although these data provide important information regarding PERT practices, they do not measure the impact of their availability on all PE patients. Our study was deliberately designed to compare outcomes of all patients with significant PE, irrespective of PERT activation, in efforts to capture both beneficial and harmful effects of PERT availability.

Arguably, the most important take-away from this analysis is the decrease in 30-day/inpatient mortality in the PERT era cohort. This was not only noted in the entire cohort, but was magnified when comparing intermediate and high-risk patients. This has not been shown in any previous study to our knowledge. Possible explanations for this reduction in mortality include decrease in major/CRNM bleeding and quicker initiation of anticoagulation, which has been previously associated with reduced mortality.[18] We can only speculate on other reasons resulting in lower mortality rates. However, given the increased mortality difference in the higher risk population, it is reasonable to conclude that higher acuity patients benefitted most from this intervention. Here, we also find that the proportion of patients undergoing advanced management, although increased in the PERT era, remained relatively small (<6%). A concern raised following the emergence of PERTs was the possible overuse of invasive techniques.[10] This was not the case in our cohort. Further, PERT was involved in the care of most patients that did undergo some form of advanced therapy in the PERT era (16 of 23). Presumably, involvement of a team that includes endovascular interventionalists, surgeons, and noninvasive physicians would result in improved patient and procedure selection. This is reflected in outcomes as none of the 23 PERT era patients undergoing invasive therapy suffered inpatient/30-day mortality (Table S2). The decrease in IVC filter use in the PERT cohort, after the PREPIC II study in 2015, also hints toward better patient selection for advanced procedures.[19]

There are some important limitations in our study. Although we included all consecutive patients, this is a retrospective analysis over 3 years. Hence, there could be unknown confounders differently distributed in the two study groups. This study only included PE diagnosed on chest CT scans. Pulmonary emboli noted on echocardiograms, angiograms, or abdominal/cardiac/neck CT scans were not included. Also, patients diagnosed on outside hospital imaging were not included. When analyzing our in-house PERT registry data, about one-third of all PERT activations were in this excluded group (data not shown). The decision to not include this data was made before initiating the study, as it was logistically not feasible to acquire this data with reasonable fidelity. For patients treated with unfractionated heparin or bivalirudin − the time to first therapeutic aPTT was used for analysis. This assumes that the patient was adequately therapeutic thereafter. Similarly, any missed/held doses, switching of medications at discharge were not accounted for any patient. There were a larger proportion of patients in the PERT era who underwent cardiac biomarker testing. Whereas this could result in misclassifying intermediate risk patients as low risk, the overall patients with neither biomarker testing or echocardiography remained relatively small. Further, this would not change the statistically significant mortality difference in the entire cohort. Finally, these favorable outcomes were established in the CC PERT model. Given the differences in the composition and workflow of different PERTs these results may not entirely translate into other models.[20]

The availability of a multidisciplinary PERT was associated with decreased bleeding complications, shorter time-to-therapeutic anticoagulation, decreased use of IVC filters and decreased all-cause 30-day mortality. Until more data is available to better risk stratify PE patients to understand which patients benefit from invasive therapy, the availability of a multidisciplinary team likely results in better patient outcomes.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.043.

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