Journal of Thrombosis and Thrombolysis (2019) 47:31–40
https://doi.org/10.1007/s11239-018-1737-8

Changes in treatment and outcomes after creation of a pulmonary embolism response team (PERT), a 10-year analysis

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Published online: 21 September 2018

Abstract

Multidisciplinary pulmonary embolism response teams (PERTs) are being implemented to improve care of patients with life-threatening PE. We sought to determine how the creation of PERT affects treatment and outcomes of patients with serious PE. A pre- and post-intervention study was performed using an interrupted time series design, to compare patients with PE before (2006–2012) and after (2012–2016) implementation of PERT at a university hospital. T-tests, Chi square tests and logistic regression were used to compare outcomes, and multivariable regression were used to adjust for differences in PE severity. Two-sided p-value < 0.05 was considered significant. For the interrupted time-series analysis, data was divided into mutually exclusive 6-month time periods (11 pre- and 7 post-PERT). To examine changes in treatment and outcomes associated with PERT, slopes and change points were compared pre- and post-PERT. Two-hundred and twelve pre-PERT and 228 post-PERT patients were analyzed. Patient demographics were generally similar, though pre-PERT, PE were more likely to be low-risk (37% vs. 19%) while post-PERT, PE were more likely to be submassive (32% vs. 49%). More patients underwent catheter directed therapy (1% vs. 14%, $p = < 0.0001$) or any advanced therapy (19 [9%] vs. 44 [19%], $p = 0.002$) post PERT. Interrupted time series analysis demonstrated that this increase was sudden and coincident with implementation of PERT, and most noticeable among patients with submassive PE. There were no differences in major bleeding or mortality pre- and post-PERT. While the use of advanced therapies, particularly catheter-directed therapies, increased after creation of PERT, especially among patients with submassive PE, there was no apparent increase in bleeding.

Keywords Pulmonary embolism · Pulmonary embolism response team · PERT · Treatment · Thrombolysis

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Highlights

- Pulmonary Embolism Response Teams (PERTs) are developing around the country and world in an effort to streamline and standardize the care of patients with severe PE
- Following the introduction of a PERT at one tertiary referral hospital, significantly more patients underwent catheter directed thrombolysis, and an interrupted time-series analysis suggested a downtrend in both bleeding and mortality
- The results of this study highlight the need for additional research to determine if the creation of a Pulmonary Embolism Response Team (PERT) affects the treatment and outcomes of patients with life-threatening PE

Introduction

Pulmonary embolism (PE) is the third most common cardiovascular death in the United States [1–4]. Recent studies estimate the 30-day mortality rate at 13% [5] and large registries estimate the mortality of massive PE as high as 52% [6].

In recent years, new therapies have been developed to treat life-threatening PE and established therapies have been adapted to treat the most severe forms of PE. These include systemic intravenous thrombolysis, catheter directed thrombolysis, suction thromboembolectomy, surgical thromboembolectomy, and extracorporeal membrane oxygenation [7–13]. However, data comparing these treatments to each other are extremely limited which makes therapeutic decision-making complex and variable. Registry data suggest that advanced therapies (other than anticoagulation alone) are underused even among patients with hemodynamically unstable, "massive" PE [2].

In order to provide better care to patients with severe PE, in 2012, the first multidisciplinary pulmonary embolism response team (PERT) was formed [14–16]. The PERT is composed of experts from different specialties who convene in real time to offer rapid, multidisciplinary consultation and mobilize resources for patients with massive or submassive PE [17]. Since the creation of the PERT model, PERTs have been developed at numerous medical centers throughout the United States, Europe and South America [15, 18–22]. However, it is not yet known how the PERT approach impacts patient care and outcomes.

To determine the impact of the PERT approach, we present a longitudinal analysis of the characteristics, treatment and outcomes of patients cared for by our PERT, and compare patients treated before and after the creation of this team.

Materials and methods

We performed this study at Massachusetts General Hospital (MGH), an urban, university-affiliated, tertiary referral hospital where the first PERT was formed. To compare outcomes before and after the implementation of our PERT, we compared patients treated by our PERT between 2012 and 2016 to patients enrolled in two previous studies: the prospective safe pulmonary embolism emergency department discharge (SPEED-D) study and the similarly structured, but retrospective, SPEED-D(R) study. All studies were approved by the Human Research Committee of Partners HealthCare Inc. (2012-P-002257, 2008-P-002001).

The organization of PERT has been described previously [14–16]. Briefly, the PERT can be activated at any time via a telephone call for any patient with confirmed or suspected severe PE. A physician member of the PERT responds to the activation, and when appropriate, convenes a multidisciplinary online meeting where the case is discussed, a diagnostic and treatment plan is developed and resources (e.g. the catheterization lab or operating room) are mobilized if advanced interventions are deemed necessary.

Since inception, we have prospectively entered data for all patients for whom PERT is activated into a HIPPA-compliant, web-based registry (http://www.project-redcap.org) [23]. Study staff are automatically notified of PERT activations via email. Staff review medical records to cull demographics, comorbid illnesses, PE risk factors, presenting signs/symptoms, vital signs, imaging and laboratory findings known at the time of PERT activation, as well as detailed follow up data detailing treatments, and outcomes up to 365 days.

The SPEED-D study is a prospective non-interventional study that enrolled 298 consecutive sample of patients diagnosed with acute PE in the MGH Emergency Department (ED) from 2008 to 2012 [24]. The SPEED-D(R) study collected similar data on 248 consecutive sample of ED patients diagnosed with acute PE, with patients enrolled retrospectively from 2006 to 2008 [25]. All ED patients with radiographically confirmed PE were eligible for enrollment, regardless of PE severity. Together, these two studies represent a consecutive sample of ED patients diagnosed with PE from 2006 to 2012 at our institution.

The methods of both SPEED-D studies are described in prior publications [24, 25]. For both studies, we collected data describing patient demographics, comorbid illnesses, PE risk factors, presenting signs/symptoms, vital signs, imaging and laboratory findings available at the time of PE diagnosis, as well as detailed follow up data describing

treatments and outcomes for the first 5 days after PE diagnosis. The only difference between the SPEED-D and SPEED-D(R) study data is the availability of 30-day follow up data. These data are only available in the SPEED-D study, as these patients received follow up phone calls after prospective enrollment.

For consistency, we limited enrollment of both pre- and post-PERT patients to those who met our hospital's established criteria for PERT activation. We therefore limited the current analysis to SPEED-D, SPEED-D(R) and PERT patients with all of the following: (1) large PE burden (defined as saddle, main pulmonary artery, lobar or multiple segmental PE); (2) tachycardia (> 100 BPM) or hypotension (systolic blood pressure < 100 mmHg) or hypoxemia (SaO_2 < 90%) or troponin ≥ 0.1 ng/mL or evidence of right heart dysfunction based on echocardiogram. In addition, because the SPEED-D studies only enrolled ED patients, we limited our analysis to post-PERT patients whose activation originated in the ED.

Both pre- and post-PERT patients were classified according to PE severity, as: massive, submassive, or low-risk, consistent with published guidelines [26–28]. Massive PE included patients with a confirmed acute PE in conjunction with sustained hypotension (systolic blood pressure < 90 mmHg). Submassive PE included patients with confirmed acute PE without sustained hypotension but with evidence of right ventricular dysfunction on echocardiogram or based on biomarkers (troponin ≥ 0.1 ng/mL or NT-proBNP ≥ pg/mL). Low-risk PE included patients with confirmed acute PE who did not meet criteria for either massive or submassive PE.

Our goal was to perform a pre- and post-intervention study to assess the specific effect of the implementation of a PERT program on treatment and outcomes. Because a randomized trial of implementation of the PERT program was not possible, to account for confounding factors such as published literature or the adoption of new techniques that could affect our outcomes, we used a quasi-experimental, interrupted time series design. We divided our data into 18, mutually exclusive 6-month time periods (11 pre-PERT [8 SPEED-D and 3 SPEED-D(R)] and 7 post-PERT), from 07/2006 to 03/2016. This study design, meant to approximate an interventional study, is based on the premise that an abrupt and significant change in treatment or outcomes that occurs coincident with the implementation of PERT is likely related to the PERT, whereas a change in practice due to unmeasured confounders would be unlikely to occur both suddenly and simultaneously with PERT implementation.

Because 30-day follow up data were only available for the SPEED-D group, we limited our analysis of 30-day outcomes to 8 six-month time periods pre-PERT and 7 post-PERT. Figure 1 shows the time line of our analysis.

Our primary outcome was the use of advanced treatment. In particular, we compared the use of systemic intravenous thrombolysis, catheter directed thrombolysis, surgical thrombectomy, or any of the above advanced treatments pre- and post-PERT. We also compared the proportions of patients who had a major bleeding event (based on the International Society for Thrombosis and Heamostasis definition) or died within 30 days of PE diagnosis.

Data were exported from REDCap™ to SAS® version 9.4 (SAS Institute, Cary, NC) for analysis. We used mean ± standard deviation to summarize continuous variables and frequency with percentages to summarize categorical variables. We compared pre- and post-PERT patients using t-tests for continuous variables and Chi square tests for categorical variables. For our interrupted time-series analysis, we compared change points and the slopes of lines of best-fit across the pre- and post-PERT periods. We performed these analyses for the study population overall, and stratified by PE severity. Because the proportion of patients with submassive PE was greater in the post-PERT group, we used logistic regression adjusting for PE severity to compare our pre-PERT and post-PERT groups. To further assess potential confounding, we performed a subanalysis where we matched pre- and post-PERT patients on age (± 10 years), PE severity, active cancer status, lowest SBP (± 10 mmHg) and lowest SaO_2 category (< 90 or ≥ 90) at time of presentation. For all analyses, a two-sided p-value < 0.05 was considered statistically significant.

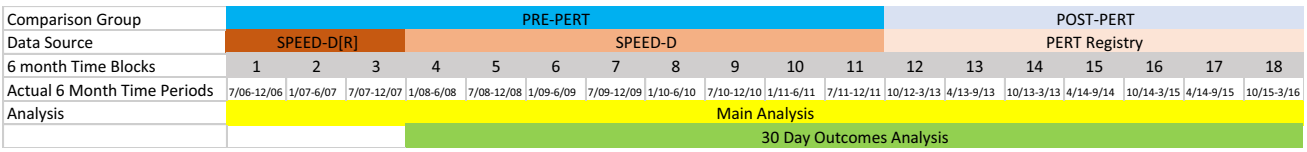

Fig. 1 Time line of enrollment and analysis. *PERT* pulmonary embolism response team

Table 1 Demographics and comorbid illnesses of enrolled pre-PERT and post-PERT patients

	Pre-PERT (n = 212)		Post-PERT (n = 228)		p value
	n. or mean	%/SD	n. or mean	%/SD	
Demographics					
Age, years (mean, SD)	59	17	61	16	0.34
Male	101	48%	120	53%	0.30
Race/ethnicity					0.001
American Indian or Pacific Islander	4	2%	0	0.0%	
Asian	1	1%	6	3%	
Black or African American	11	5%	22	10%	
Hispanic or Latino	7	3%	5	2%	
White	189	89%	186	82%	
Unknown	0	0%	9	4%	
BMI (mean, SD)	31	8	31	9	0.33
Comorbid conditions					
Anxiety or panic disorder	28	13%	38	17%	0.31
Cerebrovascular disease	10	5%	18	8%	0.17
Chronic obstructive pulmonary disease	14	7%	14	6.%	0.84
Congestive heart failure	16	8%	13	6%	0.44
Coronary heart disease	28	13%	23	10%	0.31
Malignancy					
All	89	42%	77	34%	0.076
Active	55	26%	38	17%	0.017
Renal insufficiency	1	1%	16	7%	< 0.001
Vital signs					
Highest HR	107	20	110	20	0.034
Lowest blood pressure	107	115	115	26	< 0.001
Lowest oxygen saturation	93%	6%	92%	5%	0.063

SPEED-D safe pulmonary embolism emergency department discharge, *PERT* pulmonary embolism response team, *n* number of patients, *%* percentage, *SD* standard deviation, *BMI* body mass index, *HR* heart rate

Renal insufficiency defined as creatinine clearance ≤ 30 mL/min

Results

Cohorts

We identified 212 patients before PERT and 228 patients after PERT initiation who met our inclusion criteria in the time periods we examined. (Table 1). The two cohorts were similar in age (59 ± 17 vs. 61 ± 16 years) and gender (52% vs. 47% female), but the pre-PERT cohort had a higher percentage of Caucasians (89% vs. 82%). The mean BMI was similar (31 ± 8 vs. 31 ± 9). The most common comorbid conditions were also similar between the two cohorts. However, the pre-PERT cohort had a higher percentage of patients with active cancer (26% vs. 17%). Vital signs were statistically, but not clinically different in the pre- and post-PERT groups.

Figure 2 shows the severity distribution of PE between the two cohorts. In the pre-PERT cohort, the distribution was roughly equally divided among low (n = 78, 37%), massive (n = 67, 32%) and submassive (n = 67, 32%) PE. In the

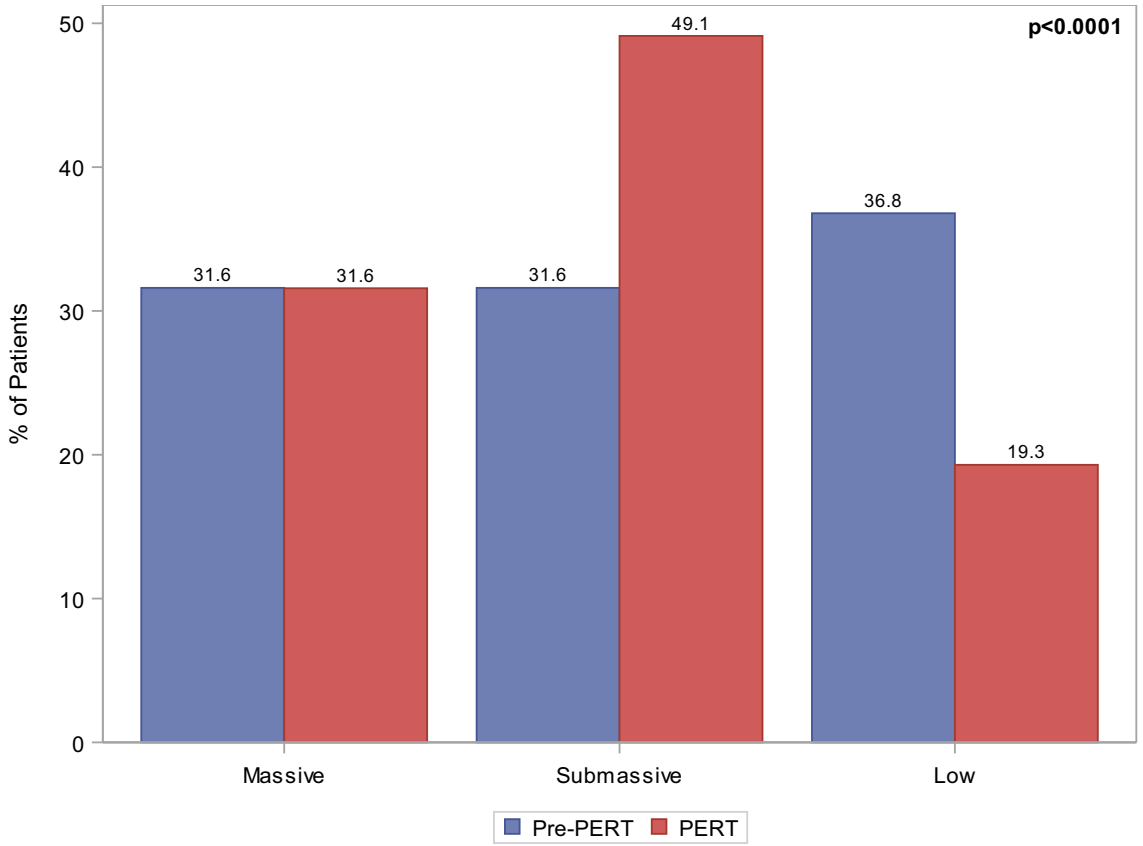

Fig. 2 Pulmonary embolism severity pre-PERT and post-PERT. *PERT* pulmonary embolism response team, % percentage

post-PERT cohort, the largest category was submassive PE, (n = 112, 49%), followed by massive PE (n = 72, 32%) and low-risk (n = 44, 19%).

Treatment

Figure 3 shows that there was no change in the proportion of patients undergoing systemic intravenous thrombolysis (10 [5%] vs. 12 [5%], p = 0.79, adjusted p = 0.50) or surgical thrombectomy (8 [4%] vs. 4 [2%], p = 0.19, adjusted p = 0.25) before or after PERT. However, the proportion of patients undergoing catheter directed therapy (10 [1%] vs. 31 [14%], unadjusted p < 0.0001, adjusted p = 0.003) and any advanced therapy (19 [9%] vs. 44 [19%], unadjusted p = 0.002, adjusted p = 0.11) was higher in the post-PERT group. Results were similar in our subanalysis where we matched on age and clinical factors: (p < 0.0001 for catheter directed thrombolysis, p = 0.072 for any advanced treatment).

Clinical outcomes

Of the 118 pre-PERT patients who had a 30-day follow-up, 6 (5.1%) suffered a major bleeding episode within 30 days compared to 13 (5.7%) among the 228 post-PERT patients (p = 0.84). Six (5.1%) patients died within 30-days in the pre-PERT group compared to 19 (8.3%) post-PERT patients (p = 0.08). In the logistic regression model adjusting for PE severity, the difference in 30-day mortality remained non-significant. Similar results were observed in the matched subanalysis (data not shown).

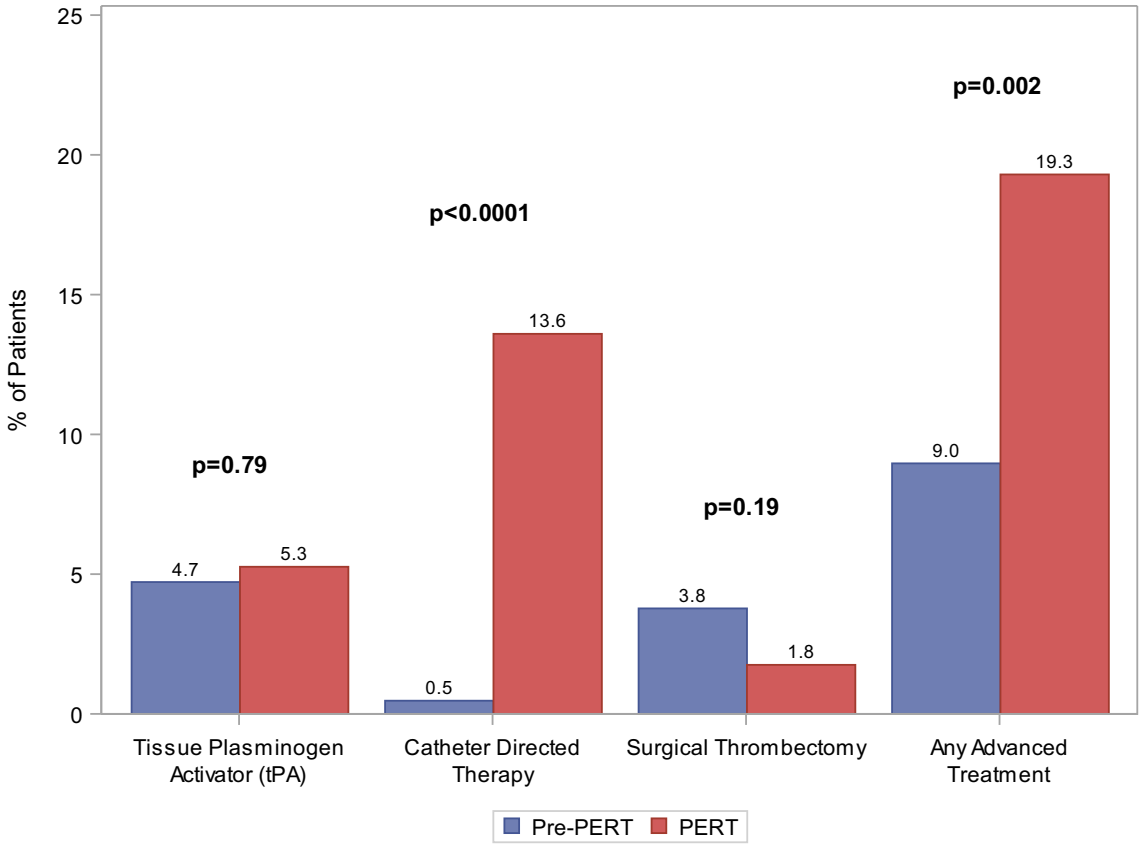

Fig. 3 Use of advanced treatments pre-PERT and post-PERT. *PERT* pulmonary embolism response team, % percentage

Interrupted time series analysis

Figure 4 shows that there was a sudden increase in the proportion of patients undergoing catheter directed thrombolysis or any advanced therapy in the post-PERT period. This was apparent for all enrolled patients (Fig. 4, panel 1) and patients with massive PE (Fig. 4, panel 2), but particularly noticeable for patients with submassive PE (Fig. 4, panel 3). There was no apparent increase in the use of catheter directed therapy or any advanced therapy among low-risk PE patients. On statistical testing, there were no statistically significant differences in the change point or slope in these time trends in either unadjusted or adjusted (for PE severity) models. Similarly, there was no apparent pattern in the occurrence of bleeding or death pre- and post-PERT (Fig. 5).

Discussion

The treatment of patients with PE is challenging. Multidisciplinary PERTs are developing across the country with an aim to streamline treatments and improve outcomes [22]. The PERT Consortium (http://www.pertconsortium.org) now has > 1400 individual members from > 100 institutions across the United States, Europe, China, and South America. Given the rapid adoption of the PERT model, determining if and how PERTs change care is important. In this report, we present the first study comparing the characteristics, treatments and outcomes of PE patients before and after the implementation of a PERT.

We found that the creation of PERT was associated with a sudden and sustained increase in the proportion of patients

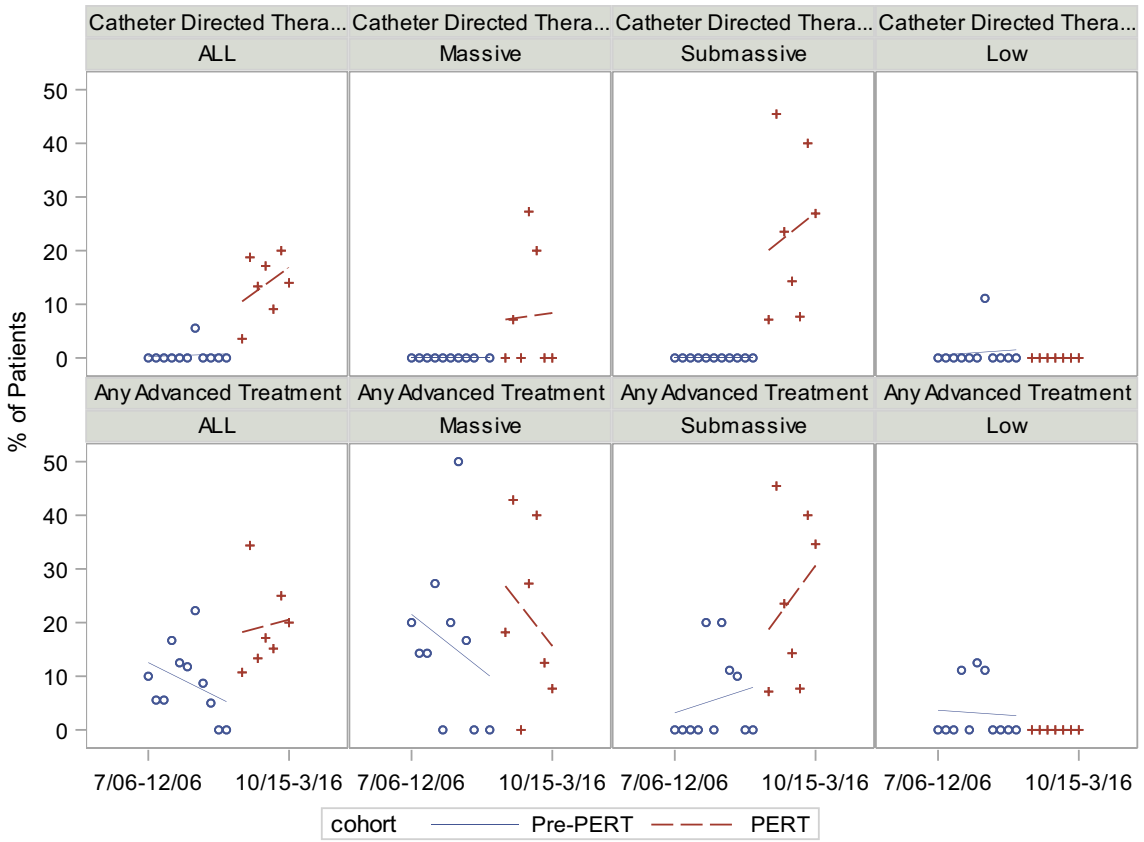

Fig. 4 Interrupted time-series analysis of the use of catheter directed therapy and any advanced treatment pre-PERT and post-PERT. *Thera* therapy, *PERT* pulmonary embolism response team. Blue dots = each blue dot represents a 6-month time period pre-PERT; red dots = each red dot represents a 6-month time period post-PERT

undergoing advanced therapy, mostly driven by an increase in the use of catheter directed therapy. This increase was generally limited to patients with submassive and massive PE. In contrast, the use of systemic intravenous thrombolysis and surgical thromboembolectomy was relatively low (≤ 5%) and remained constant pre-PERT and post-PERT. Our data suggest that the PERT process, whereby patients are rapidly assessed by multiple specialists who can quickly mobilize therapeutic resources, appears to increase the use of advanced therapies, and in particular catheter directed therapies. The fact that 19% of PERT patients were treated with some form of advanced therapy is notable, especially in the context of published registries which suggest that advanced therapies are under-utilized for PE (e.g. only 9–13% of hemodynamically unstable patients receive systemic intravenous thrombolysis) [2, 6].

Despite the increased use of advanced therapies, and in particular catheter directed therapy, we found no increase in the rate of major bleeding or mortality post-PERT. We recognize that an increase use of advanced therapies, even if not associated with bleeding, is not necessarily equivalent to improved care. Further studies of patient outcomes including morbidity and mortality are necessary.

The increase in advanced therapies we observed may reflect the "safety in numbers" phenomenon. Many of the therapies for patients with massive PE carry a high risk of potential complications, and the submassive PE group where we saw the greatest increase is the subgroup of patients for which the current evidenced-based guidelines are most

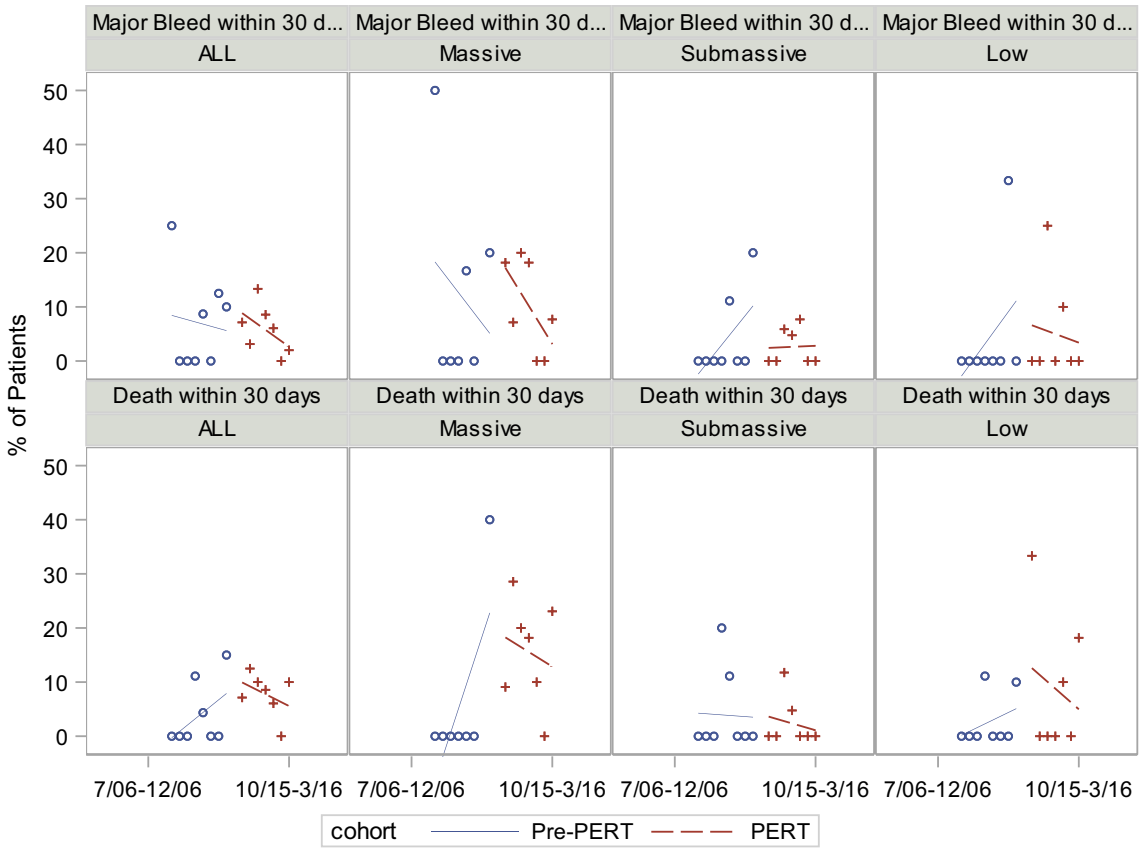

Fig. 5 Interrupted time-series analysis of major bleeding and death pre-PERT and post-PERT. *PERT* pulmonary embolism response team. Blue dots = each blue dot represents a 6-month time period pre-PERT; red dots = each red dot represents a 6-month time period post-PERT

lacking. Having the support and assistance of colleagues when choosing these therapies may enable providers to make those decisions more readily. We did consider the possibility that the increase in catheter directed therapy we observed was unrelated to PERT, but rather due to changes in practice patterns over time. For example, the availability and awareness of new catheters may have confounded our results. However, our interrupted time series analysis shows that the increase in catheter directed therapy was exactly coincident with the launch of PERT, although these therapies have been well described in the literature since the 1990s, with meta-analyses published as early as 2009 [29]. Similarly, the change we saw is not attributable to other publications, such as the ULTIMA or SEATTLE-II studies, as the increase we saw with PERT data predated these publications by several years [8, 13].

Our analysis has several potential limitations. We recognize that randomized assignment to PERT or no-PERT would represent the gold standard approach to understanding the impact of PERT. However, randomized clinical trials are difficult to conduct for programmatic changes such as PERT, so we used a quasi-experimental interrupted time-series in order to approximate a clinical trial. Also, our best available pre-PERT data was limited to Emergency Department patients, so our results may not reflect the impact of PERT on inpatients. However, the majority of PERT activations

originate from the ED (58%), so we believe our results reflect the majority of PERT patients and PE patients in general [15]. Furthermore, the frequency of treatments used in the current analysis is similar to those used in a recent analysis of a combined group of ED and inpatient PERT activations, so we believe our results are likely generalizable [15]. Our post-PERT group did include a greater proportion of submassive PE patients. However, we adjusted for this difference in several ways, with consistent results, so we do not feel this accounts for the significant increase in the use of advanced therapies post-PERT. Our study was performed in a large tertiary academic medical center and may not apply to community hospitals, where many PERTs are forming. Finally, we were not able to include an analysis of the cost of care or length of stay before and after PERT, nor were we able to assess the effect of PERT on patient quality of life. These are important topics and should be explored in future analyses.

Conclusion

Implementation of a PERT increases the use of advanced therapies, especially catheter-directed therapies, for patients with massive and submassive PE, with no associated change in bleeding or mortality. PERT programs appear to improve access to advanced therapies and may improve outcomes for patients with severe PE.

Acknowledgements The authors thank Janet McClintic, MHA, for the administrative support she provided for this work. They thank the employed research staff of the Center for Vascular Emergencies for their assistance with data collection: Erin Deadmon and Nicholas Giordano. They also greatly appreciate the efforts of the clinical fellows who contributed to the care of pulmonary embolism response team patients and the collection of data used in this manuscript: Michael Nguyen Young, Rasha Fahad Al-Bawardy, Mazen Albaghdadi, and Jorge Borges. None were compensated for their contributions.

Author contributions RR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Rosovsky, Chang, Kabrhel. Acquisition, analysis, or interpretation of data: Rosovsky, Chang, Rosenfield, Channick, Jaff, Weinberg, Sundt, Witkin, Rodriguez-Lopez, Parry, Harshbarger, Hariharan, Kabrhel. Drafting of the manuscript: Rosovsky, Chang and Kabrhel. Critical revision of the manuscript for important intellectual content: Rosovsky, Chang, Rosenfield, Channick, Jaff, Weinberg, Sundt, Witkin, Rodriguez-Lopez, Parry, Harshbarger, Hariharan, Kabrhel. Final approval of the manuscript: Rosovsky, Chang, Rosenfield, Channick, Jaff, Weinberg, Sundt, Witkin, Rodriguez-Lopez, Parry, Harshbarger, Hariharan, Kabrhel. Statistical analysis: Chang.

Compliance with ethical standards

Conflict of interest Chang, Channick, Weinberg, Witkin, Parry, Harshbarger, Hariharan declared that they have no conflict of interest. Rosovsky discloses the following relationships: grant recipient from Bristol Meyer Squibb and Janssen Pharmaceuticals; consultant to Bayer. Rosenfield discloses the following relationships: consultant to: Cardinal Health and SurModics; grants/contracts with Abbott Vascular, Atrium, Lutonix/BARD, and The Medicines Company; equity with Access Closure, Inc., and AngioDynamics/Vortex; personal compensation from Cook, HCRI, and The Medicines Company; board member with VIVA Physicians. Jaff discloses the following relationships: non compensated advisor to Abbott Vascular, Boston Scientific, Cordis, and Medtronic; equity with Vascular Therapies, PQ Bypass, Valiant Medical, and Primacea; board Member with VIVA Physicians (a 501 c 3 not-for-profit education and research). Sundt discloses the following relationship: consultant to Thrasos Therapeutics. Rodriguez-Lopez discloses the following relationships: Grant Support-Actelion pharmaceuticals. Consulting- Gilead pharmaceuticals. Kabrhel discloses the following relationships: consultant to Diagnostica Stago, Janssen Pharmaceuticals, Siemens, Pfizer, and Portola Pharmaceuticals; grant recipient from Diagnostica Stago, Siemens Healthcare, Janssen Pharmaceuticals, and Boehringer-Ingelheim.

Informed consent Informed consent was not necessary or obtained as this was part of our program's quality assurance/quality initiative and was a non interventional study.

Research involving human participants All studies were approved by the Human Research Committee of Partners HealthCare Inc. (2012-P-002257, 2008-P-002001).

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