



Vancouver General Hospital Pulmonary Embolism Response Team (VGH PERT): initial three-year experience

Équipe d'intervention en cas d'embolie pulmonaire de l'Hôpital général de Vancouver (VGH PERT): expérience initiale sur trois ans

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Abstract

Purpose *Clinical equipoise exists with the use of novel reperfusion therapies such as catheter-directed thrombolysis in the management of patients presenting to hospital with high risk pulmonary embolism (PE). Therapeutic options rely on clinical presentation, patient*

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factors, physician preference, and institutional availability. We established a Pulmonary Embolism Response Team (PERT) to provide urgent assessment and multidisciplinary care for patients presenting to our institution with high-risk PE.

Methods *Data were retrospectively collected from PERT activations between January 2016 and December 2018. Chi square tests were used to determine differences in mortality across the three years of study. Logistic regression was used to evaluate 30- and 90-day mortality and occurrence of major bleeds between those receiving anticoagulation alone (AC) and those receiving advanced reperfusion therapy (ART).*

Results *There were 128 PERT activations over three years, the majority originating from the emergency department. Eighty-five percent of activations were for submassive PE, with 56% of all activations assessed as submassive-high risk. Fifteen patients (12%) presented with massive PE. Advanced reperfusion therapy was used in 29 (23%) patients, of whom 25 (20%) received catheter-directed thrombolysis. There was an increased risk of major bleeding in the ART group compared with in the AC group (odds ratio [OR], 17.9; 95% confidence interval [CI], 4.1 to 125.0; $P < 0.001$), but no increased risk of mortality at 30 days (OR, 2.1; 95% CI, 0.4 to 9.1; $P = 0.3$). The 30-day mortality rate was 7.8%.*

Conclusion *We describe the first Canadian PERT, a multidisciplinary team aimed at providing urgent individualized care for patients with high-risk PE. Further research is necessary to determine whether a PERT improves clinical outcomes.*

Résumé

Objectif Le concept d'équilibre clinique existe lors de l'utilisation de traitements innovants de reperfusion tels que la thrombolyse in situ (ou thrombolyse par cathéter) pour la prise en charge des patients se présentant à l'hôpital avec une embolie pulmonaire (EP) à haut risque. Les options thérapeutiques s'appuient sur la présentation clinique, les caractéristiques du patient, la préférence du médecin et la disponibilité institutionnelle. Nous avons mis sur pied une Équipe d'intervention en cas d'embolie pulmonaire (PERT - Pulmonary Embolism Response Team) afin de fournir une évaluation urgente et des soins multidisciplinaires aux patients se présentant dans notre institution avec une EP à haut risque.

Méthode Nous avons récolté rétrospectivement les données concernant les activations/alertes reçues par notre PERT entre janvier 2016 et décembre 2018. Des tests de chi carré ont été utilisés afin de déterminer les différences en matière de mortalité au cours des trois années de durée de l'étude. La régression logistique a été utilisée pour évaluer la mortalité à 30 et à 90 jours ainsi que la survenue de saignements majeurs entre les patients recevant uniquement un traitement anticoagulant (AC) et ceux recevant un traitement de reperfusion avancé (TRA).

Résultats Il y a eu 128 alertes requérant l'activation de notre PERT en trois ans, la majorité provenant de l'urgence. Quatre-vingt-cinq pour cent des activations concernaient des EP submassives, et 56 % de toutes les activations ont été évaluées comme étant submassives à haut risque. Quinze patients (12 %) se sont présentés avec une EP massive. Un traitement de reperfusion avancé a été administré à 29 (23 %) patients, parmi lesquels 25 (20 %) ont reçu une thrombolyse in situ. Un risque accru de saignement majeur a été observé dans le groupe TRA par rapport au groupe AC (rapport de cotes [RC], 17,9; intervalle de confiance [IC] 95 %, 4,1 à 125,0; $P < 0,001$), mais il n'y avait pas de risque accru de mortalité à 30 jours (RC, 2,1; IC 95 %, 0,4 à 9,1; $P = 0,3$). Le taux de mortalité à 30 jours était de 7,8 %.

Conclusion Nous décrivons la première PERT canadienne, une équipe multidisciplinaire ayant pour but de prodiguer des soins personnalisés urgents aux patients avec embolie pulmonaire à haut risque. Des recherches supplémentaires sont nécessaires pour déterminer si une PERT améliore les pronostics cliniques.

Keywords pulmonary embolism · response team

Pulmonary embolism (PE) is increasing in prevalence and continues to carry significant attributable mortality.¹⁻³ Clinical equipoise exists in managing patients presenting

with acute submassive PE (defined below).⁴ Current therapeutic options for acute PE rely on clinical presentation, patient factors, physician preference, and institutional availability. As a result, contemporary management of high-risk (submassive and massive) PE involves several medical and surgical subspecialties and demands urgent co-ordinated management. Reperfusion interventions in combination with systemic anticoagulation include systemic thrombolysis, catheter-directed thrombolysis, suction thrombectomy, and surgical embolectomy. There is also increasing application of extracorporeal circulatory support.⁴⁻⁶

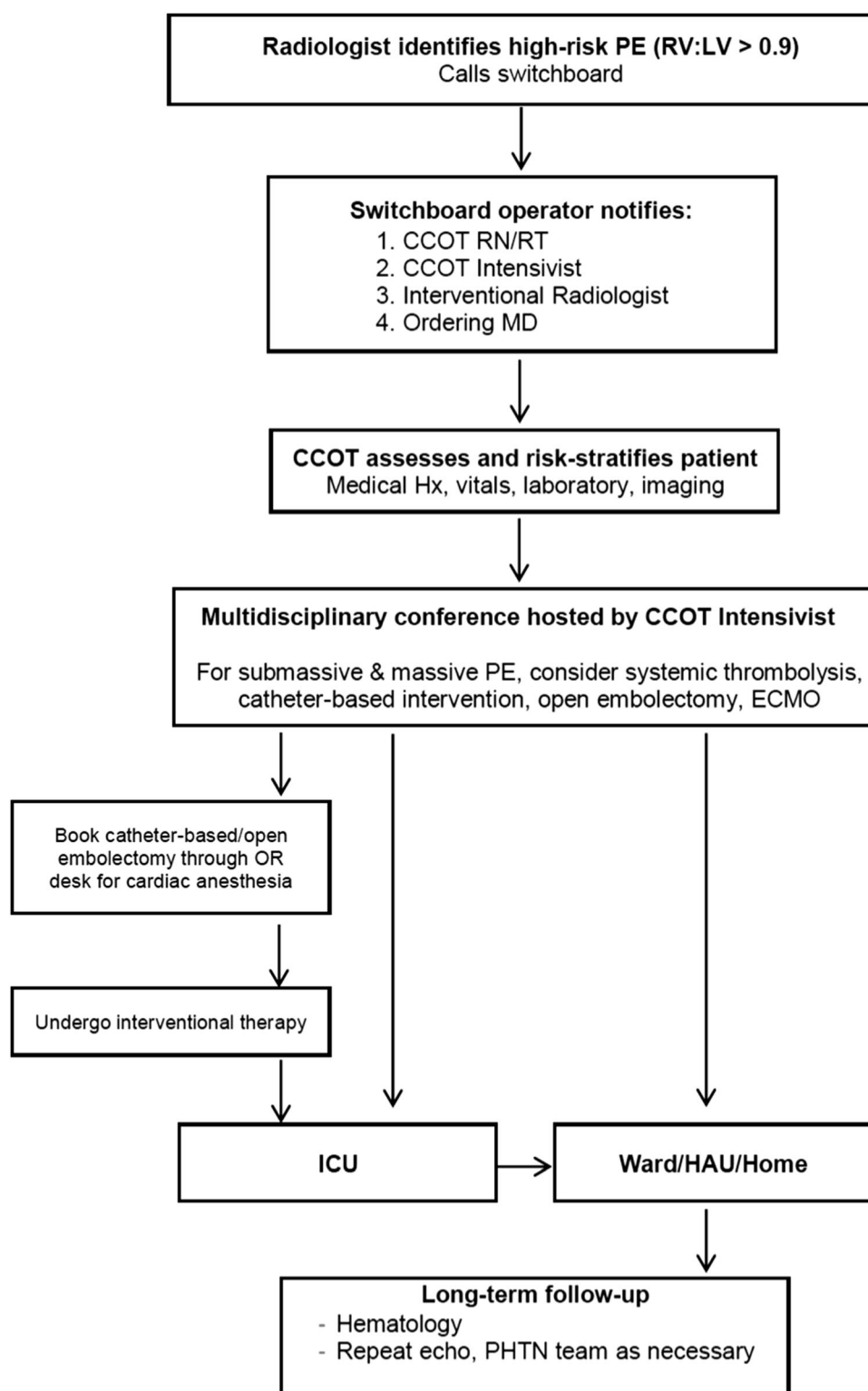
Motivated to improve patient care and inspired by the Massachusetts General Hospital Pulmonary Embolism Response Team (PERT),⁷⁻⁹ we established a rapid response team to provide urgent assessment and multidisciplinary care for patients with high-risk PE. To our knowledge, our PERT is the first in Canada; herein, we report our three-year experience of the Vancouver General Hospital (VGH) PERT.

Methods

Pulmonary Embolism Response Team algorithm

The VGH PERT is a 24/7 multidisciplinary team of specialist physicians and Critical Care Outreach Team (CCOT) registered nurses (RN) and respiratory therapists (RT) providing organized care of patients with high-risk PE confirmed on computed tomography pulmonary angiography (CTPA). This is achieved through a switchboard notification system and a dedicated teleconference line to facilitate multidisciplinary case discussion. When a high-risk PE (right ventricle:left ventricle [RV:LV] ratio ≥ 0.9) is confirmed on CTPA, the interpreting radiologist activates the PERT. The PERT RN, RT, and intensivist then assess the patient and determine the simplified pulmonary embolism severity index (sPESI) according to the European Society of Cardiology (ESC) guidelines (sPESI ≥ 1 correlates with a 30-day mortality of 11%).^{1,10} Ideally, standardized bloodwork (troponin I, brain natriuretic peptide [BNP], lactate, and arterial blood gas) is obtained and echocardiography arranged (point-of-care or formal) to enhance risk stratification. Following patient assessment, there is a teleconference of the intensivist, attending physician, interventional radiologist and/or cardiovascular surgeon. If procedural reperfusion is indicated, a cardiac anesthesiologist is involved (see Electronic Supplementary Material [ESM]; eFig. 1). Patients are subsequently managed in a critical care unit with formal hematology consultation (Fig. 1).

Fig. 1 PERT activation algorithm. CCOT= Critical Care Outreach Team; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; HAU = high acuity unit; LV = left ventricle; PERT = pulmonary embolism response team; PHTN = pulmonary hypertension; RN = registered nurse; RT = respiratory therapist; RV = right ventricle; RV:LV = ratio of ventricular diameters; sPESI = simplified pulmonary embolism severity index



Data collection

The University of British Columbia Clinical Research Ethics Board approved data collection and analysis (H16-02541). Pulmonary Embolism Response Team activations

from January 2016 to December 2018 were retrospectively identified using PERT consult forms. Only patients with CTPA-confirmed PE were included in the analysis. Patient assessment time, clinical history, and vital signs were obtained from the consult forms, which were completed by

Fig. 2 Classification of pulmonary embolism (PE) severity

Classification	Hemodynamic Instability ^a	sPESI ≥ 1 ^b	RV Dysfunction ^c	Cardiac Biomarkers ^d
Massive	+	$\pm^e$	+	$\pm^e$
Submassive-High	–	$\pm$	+	+
Submassive-Low ^f	–	$\pm$	$\pm$	$\pm$
Low	–	–	–	–

^aHemodynamic instability defined according to European Society of Cardiology guidelines.¹

^bsPESI =simplified pulmonary embolism severity index; sPESI ≥ 1 indicates a 30-day mortality risk 10.9% (95% confidence interval, 8.5 to 13.2).

^cRV = right ventricle; RV dysfunction defined on transthoracic (TTE) or transesophageal (TEE) echocardiogram as RV dilation, septal flattening, end diastolic RV:LV diameter ratio ≥ 0.9 or hypokinetic RV free wall. On computed tomography pulmonary angiography (CTPA), RV dysfunction is defined as an RV/LV diameter ratio ≥ 0.9 .

^dElevated cardiac troponin I as a marker of myocardial injury and/or elevated brain natriuretic peptide (BNP) as a result of heart failure due to RV dysfunction.

^eNeither calculation of sPESI nor measurement of cardiac biomarkers was necessary in patients with hemodynamic instability and PE confirmed on CTPA or RV dysfunction on TTE or TEE.

^fSubmassive-low risk PE defined as one of RV dysfunction or elevated cardiac biomarkers despite a sPESI of 0, or sPESI ≥ 1 with one or none of RV dysfunction or elevation in cardiac biomarkers.

the PERT RN at the time of activation. The medical history, investigations, and outcomes were obtained from medical records. Data were entered into REDCap (www.project-redcap.org), a web-based application that is Health Insurance Portability and Accountability Act-compliant. Case Report (CARE) guidelines were followed.¹¹

Definitions

We created a novel classification (Fig. 2) for patients with radiologically confirmed PE using the American Heart Association⁵ nomenclature of massive and submassive PE

and incorporating refined risk stratification of the ESC.¹ *Massive PE* was defined as a PE with hemodynamic instability as defined by the ESC (cardiac arrest, obstructive shock, or persistent hypotension).¹ *Submassive PE* was a PE without hemodynamic instability but with imaging and/or biochemical evidence of RV strain, regardless of sPESI. These patients were further subdivided into submassive-high risk (RV dysfunction on CTPA or echocardiography and biochemical evidence of myocardial injury or heart failure defined by positive troponin I or BNP, respectively) and submassive-low risk (either imaging or

biochemical evidence of RV strain, or *no* evidence of RV strain but sPESI ≥ 1).

Treatment

Anticoagulation alone (AC) refers to therapeutic administration of heparin, warfarin, low molecular weight heparin, or direct oral anticoagulant. Advanced reperfusion therapy (ART) is defined as $\geq$ one of systemic intravenous thrombolysis, catheter-directed thrombolysis (CDT), suction thrombectomy, surgical embolectomy, or extracorporeal membrane oxygenation (ECMO), typically in addition to AC. Systemic intravenous thrombolysis refers to the administration of 100 mg recombinant tissue plasminogen activator (rt-PA). Catheter-directed thrombolysis is defined as placement of infusion catheter(s) into the pulmonary artery for administration of rt-PA as per institutional protocol. Inferior vena cava (IVC) filter insertion and retrieval were recorded, though not considered a reperfusion strategy.

Outcomes

We recorded mortality at 30 and 90 days, and major bleeding events in accordance with established guidelines.¹²

Statistical analysis

Continuous variables were presented as mean (standard deviation [SD]) or median [interquartile range (IQR)], while categorical variables were presented as counts and percentages. Chi square tests were used to determine differences in mortality between years of study. Univariate logistic regression was used to compare 30- and 90-day mortality, and occurrence of a major bleed between those receiving AC and ART. We report the estimate of effects as odds ratios (OR) with 95% confidence intervals (CI) as well as their corresponding *P* value for a difference from 1. Because the number of events was small, no adjustments were made for differences in baseline patient characteristics and thus all OR presented are unadjusted. Data were analyzed in Excel (Microsoft, Seattle, WA, USA) and R statistical software (version 3.5.3; R Foundation for Statistical Computing, Vienna, Austria).¹³

Results

There were 128 activations of the VGH PERT over three years, 36 in 2016, 45 in 2017, and 47 in 2018. The majority originated from the emergency department (78% annually), with the remainder arising from the intensive care unit,

medical wards, and surgical wards. There were no significant differences in the number or location of activations between years. The provider initiating the activation was not consistently documented; however, where indicated, was most commonly a radiologist and occasionally an emergency physician. One activation was based on clinical suspicion, but the CTPA was negative for PE. Eight patients were referred and transferred to VGH for management of a PE diagnosed at the referring hospital.

Baseline data are displayed in Table 1. The mean (SD) age of patients was 63 (16) yr, and 58% were male. The majority (85%) of activations were for submassive PE, with 56% for submassive-high risk PE. Fifteen (12%) patients presented with massive PE, ten of whom had a cardiac arrest at some point during their course. Brain natriuretic peptide was measured in 84 (66%) patients, troponin I in 122 (95%), and lactate in 50 (39%). Eighty-three percent of all activations had a sPESI ≥ 1 , as did 83% of the submassive-high risk cohort. Formal transthoracic or transesophageal echocardiography was performed in 70 (55%) patients during their admission and 46 (66%) of those were abnormal with one or more of septal flattening, RV dysfunction, pulmonary hypertension, or clot-in-transit. Fifty-one (71%) patients with submassive-high risk PE had an echocardiogram. Of 128 CTPA-confirmed PEs prompting activation, 106 (83%) had RV strain (RV:LV ≥ 0.9 and/or septal flattening) on the CTPA report.

The time from activation to assessment was documented on the PERT consult form for 118 (93%) patients. The median [IQR] response time was 17 [10–23] min. The distribution of treatment by PE severity is presented in eFig. 2 (ESM). Three patients did not receive reperfusion therapy—two were palliated and one received an IVC filter alone because AC was contraindicated. The majority (75%) of patients received AC alone. Advanced reperfusion therapy was used in 29 (23%) patients, 18 (25%) with submassive-high risk and 11 (73%) with massive PE. Ten patients received systemic thrombolysis, three of whom received half dose rt-PA (50 mg). Two of these patients went on to receive veno-arterial ECMO while the third developed a massive hemothorax post-cardiopulmonary resuscitation, which may have influenced the decision to withhold full dose. Catheter-directed thrombolysis was used in 25 (20%) patients, six of whom also received systemic rt-PA. Nineteen patients (15%) received IVC filters, of which 16 were retrieved, one was unsuccessfully retrieved, and two were lacking follow-up documentation.

Outcomes

There were 13 deaths, with no difference in 30- or 90-day mortality between years (*P* = 0.85, *P* = 0.99, respectively). Thirty-day mortality was not increased for patients treated

Table 1 Baseline characteristics organized by PE severity

PE severity	Overall (<i>n</i> = 128)	Low (<i>n</i> = 4)	Submassive-low (<i>n</i> = 37)	Submassive-high (<i>n</i> = 72)	Massive (<i>n</i> = 15)
Age (yr)	63 (16)	63 (9)	60 (16)	65 (16)	64 (15)
Comorbidities/risk factors					
Cardiopulmonary disease	60 (46.9)	3 (75.0)	20 (54.1)	30 (41.7)	7 (46.7)
Malignancy	41 (32.0)	0 (0.0)	12 (32.4)	25 (34.7)	4 (26.7)
Trauma	11 (8.6)	0 (0.0)	5 (13.5)	4 (5.6)	2 (13.3)
Hospital/surgery within 30 days	38 (29.7)	1 (25.0)	17 (45.9)	16 (22.2)	4 (26.7)
HR, beats·min ⁻¹	95 (19)	88 (13)	90 (19)	95 (17)	114 (16)
SBP, mmHg	130 (22)	151 (23)	132 (20)	132 (21)	111 (27)
Cardiac arrest	10 (7.8)	0 (0)	0 (0.0)	0 (0.0)	10 (66.7)
Supplementary oxygen	80 (62.5)	0 (0)	20 (54.1)	45 (62.5)	15 (100.0)
BNP > 150 ng·L ⁻¹ *	42	0	1	38	3
Troponin I ≥ 0.02–0.181 µg·L ⁻¹ *	84	0	1	69	14
Lactate > 1.6 mmol·L ⁻¹ *	22	0	0	10	12
sPESI score					
0	22 (17.2)	4 (100)	6 (16.2)	12 (16.7)	0 (0)
1	51 (39.8)	0 (0)	20 (54.1)	30 (41.7)	1 (6.7)
2	32 (25.0)	0 (0)	6 (16.2)	22 (30.6)	4 (26.7)
3	21 (16.4)	0 (0)	5 (13.5)	8 (11.1)	8 (53.3)
4	2 (1.6)	0 (0)	0 (0)	0 (0)	2 (13.3)
IVC filter	19 (14.8)	0 (0.0)	5 (13.5)	11 (15.3)	3 (20.0)
TTE or TEE	70 (54.7)	1 (25.0)	10 (27.0)	51 (70.8)	8 (53.3)

Table 2 Overall outcomes and outcomes according to pulmonary embolus severity

PE severity	Overall (<i>n</i> = 128)	Low (<i>n</i> = 4)	Submassive-low (<i>n</i> = 37)	Submassive-high (<i>n</i> = 72)	Massive (<i>n</i> = 15)
30-day mortality	10 (7.8)	0 (0.0)	2 (5.4)	4 (5.6)	4 (26.7)
90-day mortality	13 (10.2)	0 (0.0)	3 (8.1)	6 (8.3)	4 (26.7)
Number of days from activation to death	19.2 (20.5)	–	23.0 (15.9)	26.0 (25.6)	6 (8.7)
Major bleed	10 (7.8)	0 (0.0)	0 (0.0)	5 (6.9)	5 (33.3)

Variables are presented as *n* (%) or mean (standard deviation). Major bleed is defined by International Society of Thrombosis and Haemostasis guidelines as a fatal bleed, bleeding in a critical location (e.g., intracranial), hemoglobin drop of at least 20 g·L⁻¹ or requiring ≥ 2 units packed red blood cell transfusion.¹²

with ART compared with AC (OR, 2.1; 95% CI, 0.4 to 9.1; *P* = 0.34). Three deaths occurred in patients receiving ART and the remainder were in the context of refractory shock and multiorgan failure, or limitation of care due to advanced age or malignancy (Tables 2, 3).

Ten patients suffered cardiac arrest, five having return of spontaneous circulation prior to PERT activation, three undergoing CPR at the time of activation (one cannulated on veno-arterial ECMO), and two deteriorating to cardiac arrest post activation resulting in the initiation of veno-arterial ECMO. Three patients died, one from recurrent cardiac arrest following ART (suction embolectomy) and

two patients were palliated at the time of diagnosis. Seven of the ten patients received ART, and all but one patient survived. One patient had a brief cardiac arrest with immediate stabilization and was treated with AC alone.

There was a significantly increased risk of major bleeding in the ART group compared with the AC group (OR, 17.9; 95% CI, 4.1 to 125.0; *P* = < 0.001). Of ten patients with major bleeds, eight had received ART. Bleeding events included gastrointestinal, retroperitoneal, and vaginal bleeding as well as a liver laceration and rib fractures following CPR and three catheter insertion site

Table 3 Outcomes following PERT activation according to treatment strategy

PE severity	AC (<i>n</i> = 96)	ART (<i>n</i> = 29)	No reperfusion therapy (<i>n</i> = 3)	OR* (95% CI); <i>P</i> value
30-day mortality	5 (5.2)	3 (10.3)	2 (66.7)	2.1 (0.4 to 9.1); 0.34
90-day mortality	8 (8.3)	3 (10.3)	2 (66.7)	1.3 (0.3 to 4.7); 0.75
Number of days from activation to death	27.9 (21.4)	7.3 (10.1)	2.0 (0.0)	–
Major bleed	2 (2.1)	8 (27.6)	0 (0.0)	17.9 (4.1 to 125.0); < 0.001

hematomas. Fatal bleeding occurred in one patient suffering an intracranial hemorrhage following CDT.

Discussion

We describe the first three years' experience of the first Canadian PERT. The majority of activations were from the emergency department for submassive-high risk and massive PE. Eight referrals were from community hospitals for consideration of ART. There were approximately four activations per month over the three-year period. Our PERT was designed to be activated by radiologists, but activations were occasionally initiated by other providers. Several patients did not have an increased RV:LV ratio on the CTPA report, indicating clinical discretion by clinicians to activate the PERT in the context of clinical correlation to radiologic diagnosis of PE. In other studies, PERTs are activated by any physician with or without radiographic PE confirmation, showing that there are multiple feasible activation mechanisms.^{7,14,15}

Our institutional use of ART is higher than reported in pre-PERT registry literature, but falls within the mid-range (16–46%) of other published PERTs.^{5,7} Catheter-directed thrombolysis was used in 20% of cases, representing the upper limit of published use by existing PERTs (0–20%).^{7,14,15} Our rate of major bleeds (8%) falls within the published range (5.7–14%).^{7,14,15} In contrast to other PERTs,¹⁴ we described an increased risk of major bleeds with ART; however, the wide CI limits our ability to draw precise inference. In addition, the small number of events precludes adjustment for relevant patient variables and we cannot ascertain the independent effect of ART on major bleeds. Future larger studies should examine this association. The use of ART compared with AC alone was not associated with increased 30-day mortality.

Our 30-day mortality of 8% is less than registry data (13.3%) and a multicentre analysis of American PERTs (16%, range 9–44%).^{14,16} Our 30-day mortality for massive PE is comparable to patients with massive PE in these studies; however, our submassive PE mortality is lower. Perhaps there is a particular benefit to those with submassive PE, where no clear guidelines exist and ART

has traditionally been underused. We hypothesize that early recognition, a team-based approach, and ART may contribute to improved mortality particularly in submassive PE. Further studies should assess this hypothesis as the comparisons here are of separate populations and are exploratory by nature. The PERT Consortium data highlight the variability in patient and PERT characteristics, therapies and outcomes, and we echo their call for further study to help understand these differences.¹⁴

This case series has several limitations. It is retrospective, and thus reliant on the quality and completeness of PERT consult forms and medical records. For many clinical variables (vitals, troponin I, lactate, BNP) we do not have baseline values or trends. The use and timing of formal echocardiography was inconsistent and documentation of findings from point-of-care ultrasound assessments at the time of diagnosis were insufficient to include in the analysis. Adherence to the use of formal echocardiography is an area for potential improvement to assess for acute and chronic RV dysfunction, pulmonary hypertension, and ultimately risk of chronic thromboembolic pulmonary hypertension. We did not have a pre-PERT comparison group and were unable to determine whether we captured all patients presenting with high risk PE during this time period. This single-centre description of a PERT may not be generalizable to other institutions with different resources.

The VGH PERT is the first in Canada to provide multidisciplinary care to patients presenting with high risk PE. Operationalizing a PERT can be challenging, requiring engagement from several disciplines, and further research is necessary to determine whether our PERT improves short- and long-term clinical outcomes.

Author contributions Kali R. Romano, Julia M. Cory, Juan J. Ronco, and Gordon N. Finlayson contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. Gerald M. Legiehn contributed to the conception and design of the study. Jeffrey Bone contributed to the analysis of data.

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