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Demographic, clinical, and echocardiographic factors associated with residual perfusion defects beyond six months after pulmonary embolism

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ABSTRACT

Background: Residual perfusion defects (RPD) after pulmonary embolism (PE) are common.
Primary aim: This study aimed to determine the prevalence of RPD in a cohort diagnosed with PE 6–72 months earlier, and to determine demographic, clinical, and echocardiographic variables associated with RPD.
Methods: Patients aged 18–75 years with prior PE, confirmed by computed tomography pulmonary angiography 6–72 months earlier, were included. Participants (N = 286) completed a diagnostic work-up consisting of transthoracic echocardiography and ventilation/perfusion scintigraphy. Demographic, clinical, and echocardiographic characteristics between participants with RPD and those without RPD were explored in univariate analyses using t-test or Mann-Whitney U test. Multiple logistic regression analysis was used to assess the association between selected variables and RPD.
Results: RPD were detected in 72/286 patients (25.2 %, 95 % CI:20.5 %–30.5 %). Greater tricuspid annular plane systolic excursion (TAPSE) (adjusted odds ratio (aOR) 1.10, 95 % CI:1.00–1.21, $p = 0.048$) at echocardiographic follow-up, greater thrombotic burden at diagnosis, as assessed by mean bilateral proximal extension of the clot (MBPEC) score 3–4 (aOR 2.08, 95 % CI:1.06–4.06, $p = 0.032$), and unprovoked PE (aOR 2.25, 95 % CI:1.13–4.48, $p = 0.021$) were independently associated with increased risk of RPD, whereas increased pulmonary artery acceleration time was associated with a lower risk of RPD (aOR 0.72, 95 % CI:0.62–0.83, $p < 0.001$, per 10 ms). Dyspnoea was not associated with RPD.
Conclusion: RPD were common after PE. Reduced pulmonary artery acceleration time and greater TAPSE on echocardiography at follow-up, greater thrombotic burden at diagnosis, and unprovoked PE were associated with RPD.

Abbreviations: aOR, adjusted odds ratio; CTEPH, chronic thromboembolic pulmonary hypertension; MBPEC, mean bilateral proximal extension of the clot; PE, pulmonary embolism; PH, pulmonary hypertension; RPD, residual perfusion defects; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; V, ventilation; Q, perfusion.

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1. Introduction

Residual perfusion defects (RPD), as assessed by ventilation/perfusion (V/Q) scintigraphy, occur in 25–50 % of patients after pulmonary embolism (PE) [1–7]. RPD in conjunction with precapillary pulmonary hypertension (PH) corresponds to the diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH) [8]. In absence of PH, the combination of RPD and functional limitations/symptoms is referred to as chronic thromboembolic pulmonary disease [8]. Notably, there are also patients with RPD who have neither functional limitations nor symptoms, and the correlation between the extent of obstruction and severity of symptoms is limited [9].

In patients with persistent symptoms or functional limitations after PE despite adequate anticoagulant treatment for 3–6 months, current guidelines recommend echocardiography to assess the probability of PH [10,11]. If echocardiography suggests an intermediate or high probability of PH, a subsequent V/Q scintigraphy is recommended to rule out CTEPH [10]. However, V/Q scintigraphy is not recommended as a routine follow-up after PE. The clinical implications of RPD in the absence of PH is unknown. Of note, the use of V/Q scintigraphy has decreased considerably during the last decades as computed tomography (CT) pulmonary angiogram has emerged, and thus the availability and experience in some centres may be limited [12].

This study aimed to determine the prevalence of RPD, and the association of demographic, clinical, and echocardiographic variables with RPD in a cohort of patients diagnosed with PE 6–72 months earlier.

2. Material and methods

2.1. Study design and patients

This was a two-center, cross-sectional study conducted as a part of the Pulmonary rehabilitation to improve physical capacity after PE (PE REHAB) study (clinicaltrials.gov, NCT03405480). Patients were identified from the thrombosis registry (TROLL) at the Østfold Hospital and via International Statistical Classification of Diseases and related Health Problems 10th revision discharge codes (ICD I26.x) at Akershus University Hospital, Norway [13,14]. The project was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK no. 2017/1940). All participants provided written informed consent.

Subjects meeting the following inclusion criteria were eligible to participate in the study and were invited by mail or telephone:1) PE confirmed (greater than isolated sub-segmental emboli) with CT pulmonary angiogram 6–72 months prior, and 2) age 18–75 years. We excluded patients with 1) heart failure (reduced and preserved left ventricular ejection fraction) as defined by European Society of Cardiology [15], 2) significant valvular heart disease, 3) chronic pulmonary disease (Global Initiative for Chronic Obstructive Lung disease stage > 1 or total lung capacity < 80 % of predicted [16], 4) CTEPH [17], 5) pregnancy, 6) active malignancy, or 7) psychiatric or cognitive disorder resulting in failure to comply with study programme.

All participants in the PE REHAB-study were subject to a comprehensive baseline evaluation, which included clinical examination, echocardiography, and assessment of exercise capacity using the incremental shuttle walk test [18]. All participants were referred to V/Q scintigraphy at inclusion, regardless of symptoms and echocardiographic findings. The current study consists of all participants who completed V/Q scintigraphy. We reviewed computerized medical records to gather relevant information at the time of diagnosis and retrospectively estimated the Pulmonary Embolism Severity Index for each patient [19]. Unprovoked PE was defined as no antecedent (3 months) major clinical risk factor for venous thromboembolism, such as surgery, trauma, immobilization, malignancy, pregnancy, hormonal replacement therapy or oral contraceptive use. Dyspnoea at inclusion was assessed according to a modified Medical Research Council dyspnoea score [20]. All inclusions occurred between 1 January 2018 and 1 June 2022.

2.2. Scintigraphic and radiological examinations and analyses

V/Q scintigraphy was performed using 99mTechnetium-labeled macroaggregated albumin for perfusion scintigraphy and 99mTechnetium-labeled diethylene triamine pentaacetic acid aerosol for ventilation scintigraphy. Single Photon Emission Computed Tomography images were acquired using GE Discovery NM/CT 670 SPECT/CT (General Electric healthcare, Chicago, IL, USA). The images were analysed by an experienced clinical nuclear physician (DR) employed at Østfold Hospital. RPD were considered present if there was V/Q mismatch in at least one segment or two sub-segments conforming to the pulmonary vasculature, according to the European Association of Nuclear Medicine criteria [21]. The nuclear physician was blinded with regard to patient's symptoms and echocardiographic findings, but had access to CT pulmonary angiograms from time of PE diagnosis.

An experienced clinical radiologist (JG) retrospectively assessed the thrombotic burden from CT pulmonary angiograms at PE diagnosis using the mean bilateral proximal extension of the clot (MBPEC) score [22]. The proximal extension of the embolus was identified in each lung and scored as follows: sub-segmental = 1, segmental = 2, lobar = 3, interlobar arteries, main pulmonary arteries or pulmonary trunk = 4. The final MBPEC score was the mean bilateral score, rounded upwards to the nearest integer. The radiologist was blinded to patient's symptoms, as well as echocardiographic and scintigraphic findings.

2.3. Transthoracic echocardiography

We performed echocardiographic examinations using Vivid E95 (General Electric Healthcare, Horten, Norway). Images were acquired during breath-hold, and three consecutive cardiac cycles were recorded. The echocardiographic evaluation included standard measurements of the cardiac chambers and function according to current guidelines [23].

Left ventricular ejection fraction was determined using Simpson's biplane method. Left ventricular global longitudinal strain was measured using speckle tracking imaging. Left ventricular diastolic function was assessed using the ratio between trans-mitral early diastolic filling peak velocity by pulsed doppler and the average of early diastolic annular mitral velocity at the septal and lateral part by tissue velocity imaging, and left atrial volume index [23,24].

The evaluation of the right ventricle (RV) systolic function included tricuspid annular plane systolic excursion (TAPSE), tricuspid annular peak systolic myocardial velocity and two-dimensional speckle tracking strain analysis of the RV, which was performed in a RV-focused apical four-chamber view, using three segments of the RV free wall only [23]. RV isovolumetric contraction time, RV ejection time and RV isovolumetric relaxation time were recorded using tissue doppler imaging, and RV myocardial performance index, which reflects both RV systolic and diastolic function, were calculated from these three measurements with higher values reflecting more impaired function. Tricuspid regurgitation peak velocity and pulmonary artery acceleration time were used to assess pulmonary pressure.

RV strain analysis was performed using a left ventricular-designated analysis tool, and RV free wall strain was calculated as the average of peak systolic strain-values of the three segments. The diameter of the pulmonary artery was measured halfway between the pulmonary valve and the bifurcation of the pulmonary artery.

Tricuspid regurgitation peak velocity was stratified according to the European Society of Cardiology PH guidelines, i.e., $\leq$2.8 m/s, 2.9–3.4 m/s or $>$3.4 m/s corresponding to low, intermediate and high probability of PH, respectively [11]. All echocardiographic examinations were performed according to a standardized protocol. Missing values were due to limited imaging quality, as assessed by the performing physician. See Appendix A for full list of echocardiographic measurements and

calculations.

The physician (ØJ) performing and analysing the echocardiographic examinations was blinded to the results of the V/Q scintigraphy.

2.4. Statistical analysis

Normality of the data was assessed using Shapiro-Wilk's test, quantile-quantile plots and histograms, and data are reported as mean, median or proportions as appropriate. We used the two-sample *t*-test or Mann Whitney *U* test to compare continuous variables, and Fisher's exact test to compare categorical variables between those with and without RPD.

We selected variables in the multiple regression analysis based on clinical relevance and results from the univariate analysis. We included age and sex as possible confounding factors. Additionally, we included MBPEC score, as thrombotic burden at diagnosis has previously been linked to RPD [4]. Similarly, we included unprovoked PE and dyspnoea as previous studies have shown an association between these variables and RPD [4,25]. MBPEC scores were dichotomized, i.e., score 3–4 vs. score 1–2. We included TAPSE, as this is a well-documented and most utilised measurement of RV function [23]. Regarding echocardiographic markers of PH, pulmonary artery acceleration time was chosen over tricuspid regurgitation peak velocity due to its superior feasibility [26]. As time elapsed since PE is a key factor in the prevalence and extent of RPD, this was included as an independent variable [27,28]. Finally, we included the incremental shuttle walk test as an independent variable, as RPD has been linked to exercise limitations [4]. All variables were forced into the model without any statistical variable selection procedure. We performed no imputation of missing values, and thus the analysis was performed as a complete case analysis.

Linearity of the independent variables in the logistic regression models was assessed by plots of log odds against the continuous independent variables and multi-collinearity was assessed using variance inflation factor.

To assess the reliability of the interpretation of the echocardiograms, we randomly selected 5 % of echocardiograms to be evaluated by an independent physician (AD) and compared with the first examiner (ØJ). The same echocardiograms were reviewed a second time by the first examiner to assess intrarater reliability. We selected echocardiographic variables of RV function and pulmonary hemodynamics which differed between the groups. Intraclass correlation coefficient was calculated using a two-way, random effect model with absolute agreement for the interrater assessment, and a two-way, mixed-effect model with absolute agreement for intrarater assessment of reliability.

We performed a supplementary subgroup analysis of the multiple regression analysis in participants reporting dyspnoea (modified Medical Research Council dyspnoea score ≥ 1), omitting dyspnoea as an explanatory variable.

Statistical analysis was performed using Stata version 17.0 (StataCorp., College Station, TX, USA).

3. Results

A total of 1998 subjects were identified and assessed for eligibility. We excluded 970 subjects according to predefined criteria, geographical inaccessibility, or uncertainty regarding the initial radiological diagnosis (Fig. 1). Hence, we invited 1028 subjects to participate in the study. Out of 463 responders, 126 subjects were excluded due to lack of dyspnoea. However, this was only related to inclusion for the rehabilitation part of the main project. The present study cohort also includes participants without dyspnoea. A primary evaluation was completed by 333 subjects, of whom 286 participants performed V/Q scintigraphy and echocardiography.

RPD were detected in 72 of 286 subjects, i.e., a prevalence of 25.2 % (95 % CI:20.5 %–30.5 %), at median 16 months after the initial PE diagnosis (Table 1). There were no differences regarding age, sex, or body mass index between the groups. There was a higher proportion of more proximal emboli on the MBPEC score at diagnosis in those with RPD compared to those without, 76 % vs. 54 % ($p = 0.001$). Participants with RPD performed worse on the incremental shuttle walk test compared to those without RPD, median 655 m vs. 800 m ($p = 0.016$). There was no association between RPD and dyspnoea. The proportion of subjects with diagnosed hypothyroidism was higher in those with RPD than those without, 14 % vs. 6 % ($p = 0.045$), and those with RPD had longer time between onset of symptoms and diagnosis, median 5 days vs. 3 days ($p = 0.045$).

Both pulmonary artery acceleration time, 111 ms vs. 132 ms ($p < 0.001$), and tricuspid regurgitation peak velocity, 2.61 m/s vs. 2.36 m/s ($p < 0.001$), indicated higher pulmonary pressure in those with RPD than those without, while RV myocardial performance index was impaired in those with RPD compared to those without, 0.44 vs. 0.39 ($p = 0.018$) (Table 2). The main pulmonary artery diameter was slightly increased in subjects with RPD, 22.9 mm vs. 21.4 mm ($p = 0.014$). There were no differences between left ventricular systolic or diastolic function between the two groups.

When tricuspid regurgitation peak velocity was stratified according to PH guidelines, 30 % ($n = 14$) of subjects with RPD would be classified as intermediate or high probability of PH in comparison to 3 % ($n = 4$) in those without RPD (Supplementary table B.2) [11].

In the multivariable analysis, greater TAPSE (adjusted odds ratio (aOR) 1.10, 95 % CI:1.00–1.21, $p = 0.048$), greater thrombotic burden at diagnosis, as assessed by the MBPEC score 3–4 vs. 1–2 (aOR 2.08, 95 % CI:1.06–4.06, $p = 0.032$), and unprovoked PE (aOR 2.25, 95 % CI:1.13–4.48, $p = 0.021$), were associated with RPD (Fig. 2). Increased pulmonary artery acceleration time was associated with lower risk of RPD (aOR 0.72, 95 % CI:0.62–0.83, $p < 0.001$, per 10 ms).

In subgroup analysis of participants with persistent dyspnoea, the multivariable analysis revealed similar results, albeit TAPSE was no longer significantly associated with RPD (Supplementary Fig. B.1).

4. Discussion

In this cohort of PE survivors without major cardiopulmonary comorbidities, 25 % of participants had RPD at median 16 months after the initial PE diagnosis. Reduced pulmonary artery acceleration time and greater TAPSE at echocardiographic follow-up, greater thrombotic burden at diagnosis, and unprovoked PE were independently associated with RPD.

The prevalence of RPD in this cohort is comparable to that reported in previous studies [1–6]. However, the prevalence of RPD varies considerably between studies, which is probably due to different imaging techniques and diagnostic algorithms, as well as differences in elapsed time since the initial PE event. The present study cohort comprised subjects with a wide time span since the initial PE. This may impact the prevalence of RPD, as the resolution of residual thrombotic material is believed to be a dynamic process [28]. Furthermore, the present study is a part of a larger project, where one of the main aims is to determine the effect of rehabilitation in patients with persistent dyspnoea following PE, resulting in a higher number of participants with dyspnoea being recruited. It is possible that the high prevalence of dyspnoea in this cohort may have affected the prevalence of RPD, as dyspnoea and RPD have been linked in previous studies [4,6].

Increased tricuspid regurgitation peak velocity and reduced pulmonary artery acceleration time, both indicated higher pulmonary pressure in those with RPD compared to those without. RV myocardial performance index suggested impaired RV systolic and diastolic function in those with RPD compared to those without. Estimated systolic pulmonary artery pressure, which is usually derived from tricuspid regurgitation peak velocity and the estimated pressure of right atrium, has previously been explored in the setting of RPD [23]: A cohort study of 254 patients after PE reported higher systolic pulmonary artery pressure by echocardiography in those with RPD than those without, although

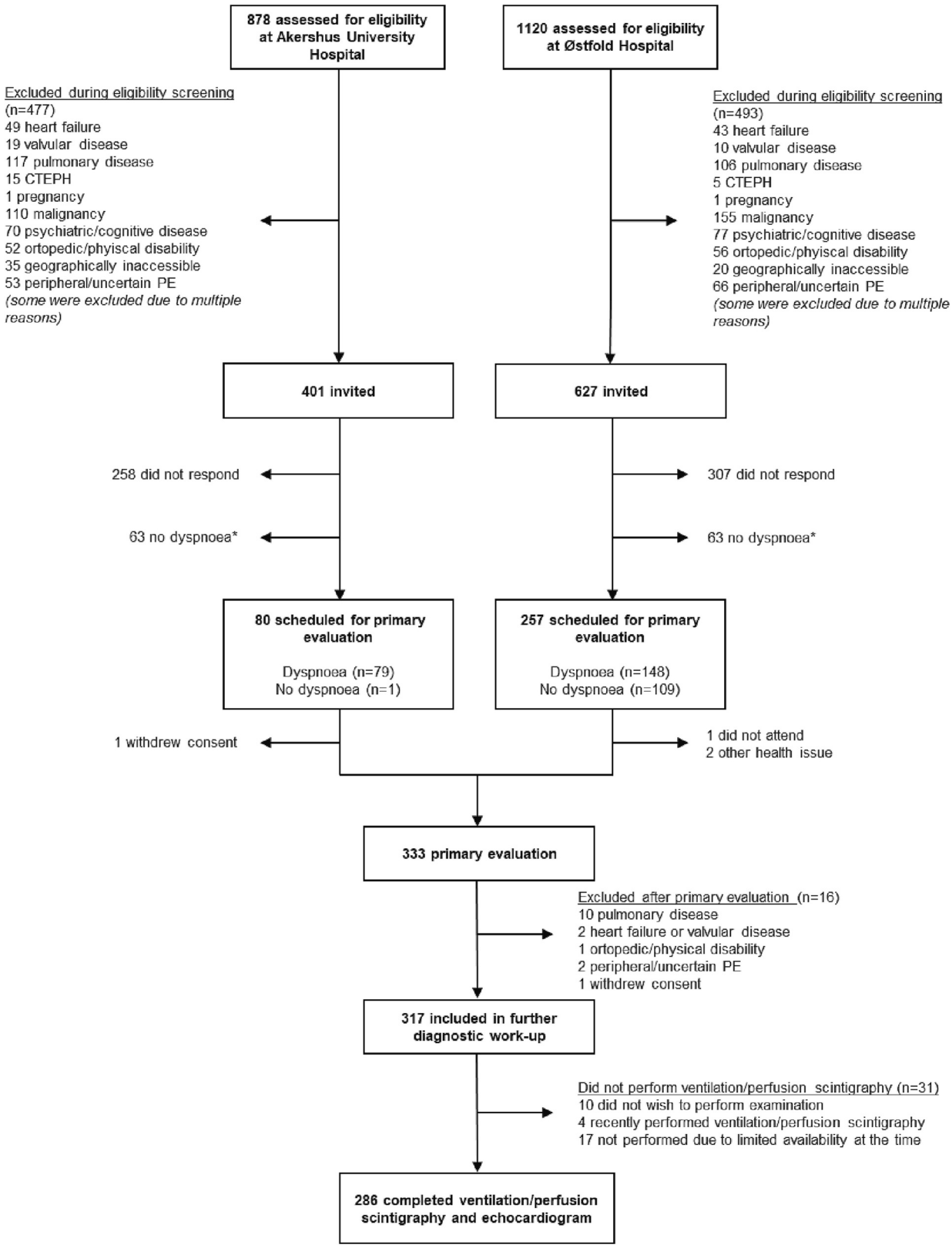

Fig. 1. Flow diagram.

**These participants were not included due to lack of dyspnoea. This was, however, only related to the rehabilitation part of the main project, and the present study cohort also includes participants without dyspnoea.*

Table 1
Demographic and historical data for those with and without residual perfusion defects (RPD) after PE. Data presented as mean (SD) unless stated otherwise.

	No RPD (n = 214)	RPD present (n = 72)	Missing (n)	P-value
Age, years (median/IQR)	59 (17)	63 (17)		0.164
Sex, males, number (%)	141 (66)	43 (60)		0.21
Body mass index, kg/m^2	29.3 (5.0)	29.4 (6.1)		0.89
Time from symptoms to PE diagnosis, days (median/IQR)	3 (6)	5 (20)		0.045
Time from PE to inclusion, months (median/IQR)	17 (16)	13 (13)		0.111
Duration anticoagulant therapy, months (median/IQR)	8 (12)	9 (8)		0.80
Dyspnoea (mMRC score) at inclusion, number (%)				0.24
0	61 (29)	14 (20)		
1	112 (53)	39 (55)		
2–4	40 (19)	18 (25)		
Incremental Shuttle Walk Test, meters (median/IQR)	800 (420)	655 (470)	2/2	0.016
Unprovoked PE, number (%)	124 (59)	52 (72)		0.049
Previous venous thromboembolism, number (%)	36 (17)	16 (22)		0.39
MBPEC score at diagnosis, number (%)			13/2	0.001
1–2	93 (46)	17 (24)		
3–4	108 (54)	53 (76)		
PESI score at diagnosis	67.9 (19)	72.5 (18)	16/7	0.095
Troponin at diagnosis, ng/L (median/IQR)	4 (12)	27 (122)	71/26	<0.001
D-dimer at diagnosis, mg/L (median/IQR)	3.6 (6.2)	6.6 (9.5)	23/5	<0.001
Comorbidities, number (%)				
Hypertension	69 (32)	26 (36)		0.57
Coronary disease	4 (2)	4 (6)		0.113
Diabetes	8 (4)	6 (8)		0.125
Hypothyreosis	12 (6)	10 (14)		0.045
Chronic Kidney Failure (GFR <60 mL/min/1.73m^2)	4 (2)	2 (3)		0.65

Abbreviations: IQR – interquartile range; GFR – glomerular filtration rate; MBPEC – mean bilateral proximal extension of the clot (1 = sub-segmental, 2 = segmental, 3 = lobar, 4 = main pulmonary arteries/pulmonary trunk); mMRC – modified Medical Research Council; PE – pulmonary embolism; PESI – pulmonary embolism severity index; RPD – residual perfusion defects.

Table 2
Echocardiographic findings for those with and without residual perfusion defects (RPD) after PE, presented as mean (SD).

	No RPD (n = 214)	RPD present (n = 72)	Missing (n)	P-value
LV ejection fraction (Simpson biplane), %	61.8 (5.1)	61.9 (4.9)		0.92
LV global longitudinal strain	−19.0 (2.2)	−19.2 (2.2)	63/24	0.60
E/E′ average	6.7 (1.9)	6.6 (1.8)	4/1	0.81
Left atrial volume index, ml/m^2	27.2 (8.8)	27.8 (8.7)	2/0	0.60
Right atrial area, cm^2	18.8 (4.5)	18.8 (4.1)	8/2	0.92
RV basal diameter, mm	37.0 (6.3)	36.3 (6.3)	18/2	0.40
RV end-diastolic area, cm^2	22.7 (4.5)	22.2 (4.6)	28/9	0.28
Main pulmonary artery diameter, mm	21.4 (0.3)	22.9 (0.4)	96/28	0.014
TAPSE, mm	24.9 (3.6)	24.9 (3.3)	1/0	0.99
RV S′, cm/s	12.7 (2.4)	12.7 (2.5)	3/0	0.88
RV myocardial performance index	0.39 (0.13)	0.44 (0.16)	15/2	0.018
RV free wall strain	−26.5 (4.0)	−26.0 (3.1)	69/20	0.44
Pulmonary artery acceleration time, ms	132 (26)	111 (26)	4/3	<0.001
Tricuspid regurgitation peak velocity, m/s	2.36 (0.25)	2.61 (0.41)	64/25	<0.001

Abbreviations: E – transmitral early diastolic filling peak velocity; E′ - Early diastolic annular velocity of the mitral valve; LV – left ventricle; RV – right ventricle; RV S′ – right ventricle tricuspid annular peak systolic velocity; TAPSE – tricuspid annular plane systolic excursion.

the time from PE to assessment was shorter than in the present study [4]. In contrast, in another smaller cohort (n = 71), using a similar approach, there was no evidence of pulmonary hypertension in subjects with RPD [2]. Neither of these two studies reported other echocardiographic measurements of RV function or hemodynamics. It is important to emphasize that our results were recorded at rest, and it is possible that PH may be more enhanced by physical activity. Other studies using a similar approach or right heart catheterisation to identify an increase of pulmonary hypertension, impaired RV function, or a dilatation of the pulmonary artery, have to the best of our knowledge not been performed in studies concerning RPD.

As only 2/3 of patients have a tricuspid regurgitation jet that allows for reliable measurement of peak velocity, current guidelines recommend the inclusion of alternative echocardiographic methods to assess PH [29]. In our cohort, both higher tricuspid regurgitation peak velocity and reduced pulmonary artery acceleration time were associated with RPD in univariate analysis. Importantly, adequate image quality for assessment of pulmonary artery acceleration was obtained in 98 % of the subjects compared to 69 % for tricuspid regurgitation peak velocity, which is in line with other studies [30].

Although borderline significant, greater TAPSE was associated with the presence of RPD in the multivariable analysis. Greater TAPSE may be due to an early adaption of the right ventricle, where the contractility improves to match the increased afterload [31]. However, this mechanism is likely only relevant in those with shorter time since PE-diagnosis.

MBPEC score 3–4 at the time of diagnosis, i.e., a more proximal location of PE, had higher odds of RPD than a more distal location (score 1–2) in the multivariable analysis. This supports previous findings that the extent of vascular obstruction at the time of diagnosis, assessed by different radiological modalities and scoring systems, is associated with RPD [4–6].

Unprovoked PE was associated with the RPD both in the univariable and the multivariable analysis. This association has also been confirmed in other studies [1,25]. Patients with unprovoked venous thromboembolism have higher risk of recurrence compared to those who have an identifiable risk factor [32]. Furthermore, these patients may differ in demographic factors, comorbidities, or may have unrecognized thrombophilia, which may in turn influence the risk for RPD [33,34].

We could not detect any association between dyspnoea and RPD in the univariable or the multivariable analysis. Dyspnoea has been linked to RPD in other studies [4,6], however, the definition of dyspnoea in these studies has not been clearly stated. In the multivariable analysis, we defined dyspnoea as a patient-reported modified Medical Research Council dyspnoea score of 2 ("*walks slower than people of the same age because of dyspnoea or has to stop for breath when walking at own pace*") or worse, as we thought this would represent a clinically relevant degree of dyspnoea. However, dyspnoea was not assessed at exertion, which might give a more precise assessment of symptoms.

Although there was a clear difference in performance on the incremental shuttle walk test in the univariate analysis, no such difference was evident in the multivariable analysis. The impact of RPD on functional limitation is unclear and the existing evidence is conflicting [4,7,9]. V/Q scintigraphy is a sensitive test, and may detect smaller perfusion defects which likely has no hemodynamic or clinical consequence.

Patients with RPD had longer time from symptom onset to diagnosis

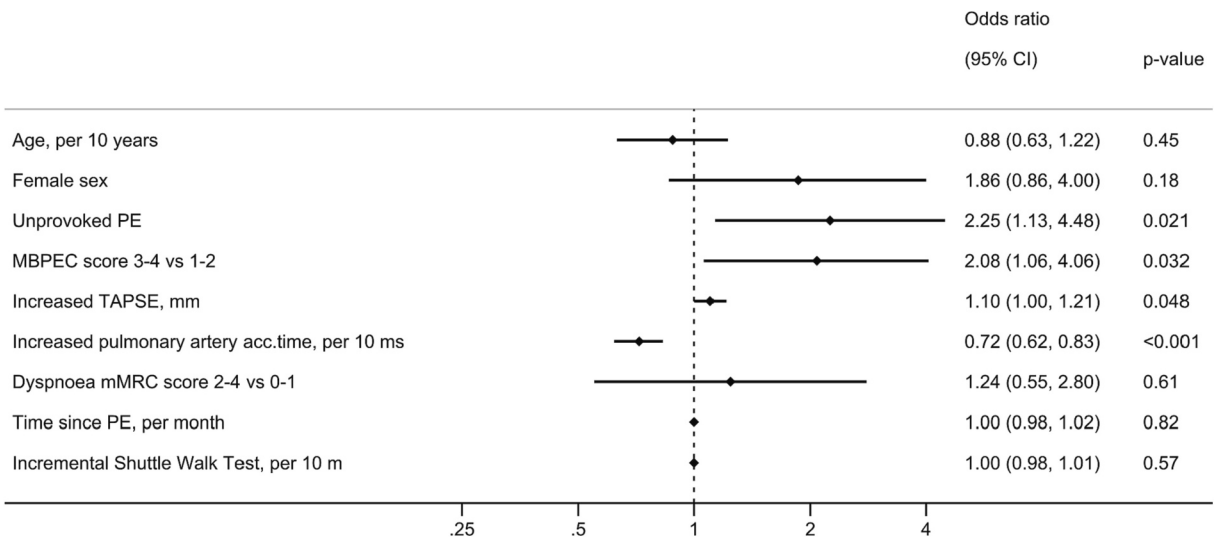

Fig. 2. Determinants of residual perfusion defects in multivariable logistic regression analysis. Data presented as adjusted odds ratios with 95 % CI and *p*-values ($N = 261$).
Abbreviations; acc – acceleration; MBPEC – mean bilateral proximal extension of the clot; mMRC – modified Medical Research Council; PE – pulmonary embolism; TAPSE – tricuspid annular plane systolic excursion.

which is in line with other studies [2,4]. Furthermore, there was a higher proportion of subjects with diagnosed hypothyroidism in the group with RPD. A similar association has been observed in patients with CTEPH, but to our knowledge not in patients with RPD [35]. Thyroid dysfunction is associated with both bleeding and thrombosis [36], and treatment with thyroxine may increase levels of von Willebrand factor [37]. However, the underlying mechanism behind this association remains unclear.

Strengths of the present study are the inclusion of a large number of subjects who all underwent V/Q scintigraphy and echocardiography, and the use of novel echocardiographic indices not previously described in studies concerning RPD. Some limitations should be noted. Although we excluded patients with pre-diagnosed CTEPH, we cannot rule out the possibility of subjects with undiagnosed CTEPH in our cohort. The exclusion of several prevalent cardiopulmonary conditions complicates direct comparison with other studies and restricts the generalizability of our results. The study cohort includes patients with and without dyspnoea. Due to the nature of the main project, recruitment was focused on those with dyspnoea, and thus the present cohort may not be representative of a general post-PE population. To address this, we performed a subgroup analysis in participants reporting dyspnoea. Our multivariable model includes variables from different points in time, which may complicate the interpretation of our findings. The echocardiographic and radiological images were not assessed by an independent core imaging laboratory. Only one physician performed the echocardiographic examinations and analyses. However, intrarater and interrater agreement of the interpretation of the echocardiographic recordings were excellent for most variables. We did not perform saline contrast during echocardiography, which could have improved the detection of tricuspid regurgitation.

In a clinical perspective, our study demonstrates that RPD are common after PE, and our findings may help clarify the impact of RPD on symptoms and functional status. Interestingly, dyspnoea and exercise capacity were not independently associated with the presence of RPD in our cohort, despite echocardiographic signs of increased pulmonary artery pressure when compared to those without RPD. A multicentre, prospective, and properly designed study to improve our knowledge and understanding of this large group of patients is warranted.

5. Conclusions

RPD were present in 25 % of PE survivors. Reduced pulmonary artery acceleration time and greater TAPSE by echocardiography, greater thrombotic burden at diagnosis, and unprovoked PE were independently associated with RPD.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

F. Klok has received research support from Bayer, Bristol-Myers Squibb, Actelion, Boston Scientific, Leo Pharma, FarmX, The Netherlands Organisation for Health Research and Development, The Dutch Thrombosis Association, The Dutch Heart Foundation and the Horizon Europe program, all outside this work and paid to his institution. K.Stavem reports consulting fees from MSD and UCB unrelated to this study. W.Ghanima reports fees for participation in Advisory board from Amgen, Novartis, Pfizer, Principia Biopharma Inc- a Sanofi Company, Sanofi, SOBI, Grifols, UCB, Argenx, Cellphire, and lecture honoraria from Amgen, Novartis, Pfizer, Bristol Myers Squibb, SOBI, Grifols, Sanofi and Bayer. W.Ghanima reports research grants from Bayer, BMS/Pfizer and UCB. A.Dhayyat, D.Rashid, J.Gleditsch, K.Steine M.Tavoly, S. Haukeland-Parker, and Ø.Jervan declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendices. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.06.004.

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