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Association between myocardial fibrosis, as assessed with cardiac magnetic resonance T1 mapping, and persistent dyspnea after pulmonary embolism

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ABSTRACT

Background: Persistent dyspnea is a common symptom after pulmonary embolism (PE). However, the pathophysiology of persistent dyspnea is not fully clarified. This study aimed to explore possible associations between diffuse myocardial fibrosis, as assessed by cardiac magnetic resonance (CMR) T1 mapping, and persistent dyspnea in patients with a history of PE.

Methods: CMR with T1 mapping and extracellular volume fraction (ECV) calculations were performed after PE in 51 patients with persistent dyspnea and in 50 non-dyspneic patients. Patients with known pulmonary disease, heart disease and CTEPH were excluded.

Results: Native T1 was higher in the interventricular septum in dyspneic patients compared to non-dyspneic patients; difference 13 ms (95% CI: 2–23 ms). ECV was also significantly higher in patients with dyspnea; difference 0.9 percent points (95% CI: 0.04–1.8 pp). There was no difference in native T1 or ECV in the left ventricular lateral wall. Native T1 in the interventricular septum had an adjusted Odds Ratio of 1.18 per 10 ms increase (95% CI: 0.99–1.42) in predicting dyspnea, and an adjusted Odds Ratio of 1.47 per 10 ms increase (95% CI: 1.10–1.96) in predicting Incremental Shuttle Walk Test (ISWT) score < 1020 m.

Conclusion: Septal native T1 and ECV values were higher in patients with dyspnea after PE compared with those who were fully recovered suggesting a possible pathological role of myocardial fibrosis in the development of dyspnea after PE. Further studies are needed to validate our findings and to explore their pathophysiological role and clinical significance.

1. Introduction

Until recently, follow-up studies of patients with pulmonary embolism (PE) have only focused on chronic thromboembolic pulmonary hypertension (CTEPH), which affects about 3–4% of PE survivors [1,2]. However, some studies suggest that up to 50% of the patients may suffer from varying degree of persistent dyspnea after an episode of acute PE without having signs of CTEPH. It has been shown that these patients have impaired exercise capacity and reduced Health Related Quality of Life (HRQoL) compared to patients with no dyspnea [3–8].

The term Post Pulmonary Embolism Syndrome (PPS) has been proposed to collectively describe the spectrum of sequelae after PE that ranges from CTEPH to unexplained persistent dyspnea and functional impairment [3,9]. Apart from CTEPH, the exact causes and underlying pathophysiology of persistent dyspnea in patients with a history of PE have not yet been properly characterized. Recently, some studies have

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concluded that cardiopulmonary abnormalities related to the acute PE episode may be an important contributing factor to the development of persistent dyspnea [10,11]. However, since cardiopulmonary abnormalities cannot always be identified, general deconditioning has also been suggested to be a potential explanatory factor for persistent dyspnea after PE [12,13].

Diffuse myocardial fibrosis has been recognized in conditions such as hypertensive heart disease, hypertrophic cardiomyopathy and idiopathic dilated cardiomyopathy, and can represent a possible causative factor for myocardial dysfunction in a variety of non-ischemic cardiomyopathies [14–18]. When using cardiac magnetic resonance (CMR), the T1 relaxation time of the tissue can be directly measured (so-called T1 mapping) to assess diffuse myocardial fibrosis [17,19–22]. Native T1 relaxation time (without contrast medium injection) is indeed increased in the presence of fibrotic myocardium [18,23]. Supplemented with T1 measurement after contrast medium injection, it is possible to calculate the myocardial extracellular volume fraction (ECV) which is strongly correlated to extracellular matrix, directly corresponding to diffuse fibrosis [24].

Acute PE induces a generalized inflammatory response to the thrombus formation [9]. Furthermore, it has been demonstrated that right ventricular inflammation after PE is likely to be caused by increased vascular resistance and associated elevated afterload [25]. Myocardial inflammation, remodeling and fibrosis are known as a continuum of closely linked processes [26]. With the use of CMR, diffuse myocardial fibrosis has been demonstrated in CTEPH, and CMR fibrosis markers have been suggested as possible diagnostic, prognostic or therapy-monitoring tools [27,28].

The primary objective of this study was to explore whether persistent dyspnea after PE is associated with increased diffuse myocardial fibrosis as assessed by CMR. The secondary objective was to explore the association between the extent of diffuse myocardial fibrosis and functional exercise capacity as measured with the Incremental Shuttle Walk Test (ISWT).

2. Material and Methods

2.1. Study design

This was a single center cross-sectional sub-study of an ongoing project evaluating the effect of pulmonary rehabilitation to improve physical capacity after PE (clinicaltrials.gov - NCT03405480) [29].

The project was approved by the Regional Committee for Medical and Health Research Ethics in Norway (REK 2017/1940) and all participants signed an informed written consent form.

2.2. Study population

Patients were identified through the Østfold Thrombosis Registry (TROLL). The TROLL registry includes all patients who have been diagnosed with and/or treated for venous thromboembolism in Østfold Hospital, Norway since 2005.

Patients who met the following inclusion criteria were invited to participate: 1) age 18–75 years; 2) objectively diagnosed PE (greater than isolated sub-segmental) by computed tomography pulmonary angiography (CTPA); and 3) 6–72 months since diagnosis of PE.

Among the exclusion criteria were pulmonary diseases including obstructive pulmonary diseases (Global Initiative for Chronic Obstructive Lung Disease stage > 1), restrictive pulmonary diseases (total lung capacity < 80%), lung cancer or pleural disease, heart failure with reduced or preserved ejection fraction, valvular heart disease, and active malignancy (Table 1). Heart failure was defined as ejection fraction (EF) < 50%. Heart failure with preserved EF was defined as the combination of diastolic dysfunction, proBNP > 300 mg/L and symptoms of heart failure. Diastolic dysfunction was evaluated by echocardiography and considered present if > 50% of the following findings were present: early mitral inflow velocity (E) and mitral annular early diastolic velocity (E') ratio > 14, septal E′ < 7 cm/s or lateral E′ < 10 cm/s, left atrial volume index > 34 mL/m2 or tricuspid regurgitation peak velocity > 2.8 m/s according to European Society of Cardiology (ESC) guidelines [30].

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
1. Age 18–75 years
2. Objectively diagnosed symptomatic PE (greater than isolated sub-segmental PE) by CTPA 6 months to 6 years before inclusion
3. Signed informed consent

Exclusion criteria
1. Patients with known pulmonary diseases including obstructive (COPD GOLD ≥ 2 = FEV1/FVC < 0.7 and FEV1 < 80%) and restrictive pulmonary diseases (total lung capacity < 80%), lung cancer or pleural disease
2. Heart failure with reduced EF (EF < 50%) or preserved EF (combination of diastolic heart failure, proBNP > 300 mg/L and symptoms).
3. Chronic thromboembolic pulmonary hypertension
4. Significant valvular heart disease
5. Patients who are unable to perform ISWT due to old age, physical disability or disease
6. Patients with history of poor compliance or any condition that would interfere with the ability to comply with the study protocol or to give informed consent e.g. history of drug abuse, excessive alcohol beverage consumption, cognitive dysfunction, or severe psychiatric disease
7. Active malignancy, i.e. receiving active antimitotic treatment or diagnosed within the past 6 months; or recurrent or metastatic; or inoperable. Patients with squamous skin cancer and basal cell carcinoma will not be excluded
8. Life expectancy<3 months
9. Pregnancy
10. General contraindications for MRI including non-compatible intracranial vascular clips, cardiac pacemaker or ICD, neurostimulator system, cochlear implant and metallic splinters in the eye.
11. Serious renal failure (GFR < 30 mL/minute)
12. Previous reactions to MRI contrast agent
13. Inability to lie in the supine position for 60 min
14. Significant arrhythmias (such as atrial fibrillation or frequent premature ventricular contractions)
15. Inability to stop breathing for periods up to 15 s
16. Body weight > 250 kg or very wide circumference

Abbreviations: PE – Pulmonary Embolism, CTPA – Computer Tomography Pulmonary Angiogram, COPD – Chronic obstructive pulmonary disease, GOLD – Global Initiative for Chronic Obstructive Lung Disease, FEV1 – Forced Expiratory Volume in one second, FVC – Forced Vital Capacity, EF – Ejection Fraction, ISWT – Incremental Shuttle Walk Test, MRI – Magnetic Resonance Imaging, GFR – Glomerular filtration rate.

Eligible patients were invited to participate and were recruited between January 1st 2018 and December 31st 2019. Based on interviews and a self-completed questionnaire, patients were classified into either of two groups: 1) dyspnea or 2) no dyspnea. This classification was performed prior to any study-related procedures. The modified Medical Research Council (mMRC) dyspnea scale was used to grade the patient's respiratory disability, ranging from 0 to 4, where 0 represents no symptoms of dyspnea and 4 represents the worst possible state [31]. Patients with the combination of new onset dyspnea after the acute PE episode that had persisted for at least 6 months, and with mMRC dyspnea scale score ≥ 1 were classified into the "dyspnea" group. All other patients were classified into the "no dyspnea" group.

All study patients underwent comprehensive investigations at inclusion including clinical assessment, biochemistry (proBNP and high sensitivity Troponin I), arterial blood gas, echocardiography, spirometry, ISWT. If no reasons for exclusion was identified at the recruitment visit, the patient was referred for V/Q-scintigraphy and CMR. Demographic and clinical data including height, weight, smoking history and comorbidity were also registered. Median time from baseline (initial) visit to completion of all study procedures was 6 weeks (IQR: 0–10 weeks).

Patients with established diagnosis of CTEPH were not invited to participate in the study. All patients were screened for pulmonary hypertension with echocardiography during the recruitment visit. Right

heart catheterization was performed if: 1) echocardiography-criteria were consistent with high probability for pulmonary hypertension according to ESC pulmonary hypertension guidelines [32]; 2) perfusion defects at ventilation/perfusion (V/Q) scintigraphy were detected; and 3) symptoms consistent with pulmonary hypertension were present. Patients who were diagnosed with CTEPH by right ventricular catheterization were excluded.

2.3. Incremental Shuttle Walk test

Sub-maximal physical capacity was measured using the ISWT [33,34] where the subject walks between two cones on a 9-meter track with a gradually increasing standardized speed as determined by audible queues. The test is complete when the subject does not cope with the speed requirement or reaches the maximum test length of 1020 m (12 min).

2.4. Computer tomography pulmonary angiography (CTPA)

CTPA images acquired at PE diagnosis were re-assessed to verify the PE diagnosis and to assess the clot burden. The CT scans had been performed according to the hospital's standard clinical procedure with a uniphase injection of low-osmolar or iso-osmolar contrast media injected through the cubital vein with a power injector. The injection rate was up to 5 mL/s (1.7 g Iodine/s) and the scanning delay was determined by continues bolus tracking of the pulmonary trunk. CT-scans were obtained with 64 or 128 slice scanners (Phillips Brilliance 64 or Phillips Ingenuity 128; Eindhoven, the Netherlands). Images were acquired in the caudocranial direction and reconstructed to 3-millimeter slices in the transversal, sagittal and coronal planes.

Mean Bilateral Proximal Extension of the Clot (MBPEC) was used to assess the clot burden using the following procedure [35]: For each lung, the most proximal extension of the embolus is identified and categorized as 1) sub-segmental, 2) segmental, 3) lobar arteries or 4) pulmonary trunk, main pulmonary arteries or interlobar arteries. MBPEC score was calculated using the mean of the category values from both lungs rounded up to the closest integer.

2.5. V/Q-scintigraphy

V/Q-scintigraphy was performed according to the EANM guideline [36] using 99mTc-labeled macroaggregated albumin (99mTc-MAA) for perfusion scintigraphy and 99mTc-labeled diethylene triamine pentaacetic acid (99mTc-DTPA) aerosol for ventilation scintigraphy. Images were acquired using a GE Discovery NM/CT 670 SPECT/CT scanner (GE Healthcare, Chicago, IL, USA). 99mTc-DTPA was inhaled through a single-use nebulizer system from Swirler (Amici Inc., Spring City, PA, USA). Chronic perfusion defect was considered positive and reported if there was ventilation/perfusion mismatch in at least one segment or two sub-segments that conformed to the pulmonary vascular anatomy.

2.6. Cardiac magnetic resonance protocol

All CMR examinations were carried out on a Siemens 1.5 T Aera magnet (Siemens Healthcare, Erlangen, Germany) according to established standards [21,22] using a surface coil in combination with the spine coil. ECG-triggered steady state free precision cine imaging was acquired during multiple breath-holds in three long axis and 10–12 consecutive short axis planes of 6 mm thickness perpendicular to the left ventricular long axis. Thirty phases were retrospectively reconstructed per heartbeat. Late gadolinium enhancement (LGE) images were acquired with a phase sensitive inversion recovery sequence with fixed inversion time of 300 ms in similar image planes. T1 images were acquired in the diastolic phase in basal and mid-ventricular short axis planes using the Modified Look Locker Imaging (MOLLI) technique according to a 5(3)3 scheme pre contrast and a 4(1)3 scheme post contrast. Post-contrast short-axis T1-mapping was acquired 15 min after the start of intravenous contrast medium injection of 0.15 mmol/kg (0.3 mL/kg) Gadoterate meglumine (Clariscan, GE Healthcare, Chicago, IL, USA or Dotarem, Guerbet, Villepinte, France) and LGE images were acquired immediately after.

2.7. CMR post processing

For volumetric evaluation of the left and right ventricle (LV and RV), endo- and epicardial contours were manually drawn in end-diastole and end-systole on short axis images. Contours were refined to minimize the difference between RV and LV stroke volumes. Presence of LGE was evaluated dichotomously (present or not present). LGE was categorized in ventricular insertion points LGE, coronary pattern mid-wall or diffuse/patchy. To be deemed positive, LGE had to be present on a minimum of two consecutive short axis slices or one short axis and one long axis slice.

Three regions of interest were manually drawn on to basal and mid-ventricular T1 maps to measure mean T1 times: 1) interventricular septum 2) left ventricular lateral wall, and 3) left ventricular lumen. Myocardial borders were carefully excluded to avoid errors due to partial volume. The reported T1 value of each region was the mean of the measured T1 on the basal and mid-ventricular slice. Hematocrit measurement was obtained immediately before CMR.

All CMR post processing was performed in Segment version 3.1 (Medviso AB, Lund, Sweden) [37]. Volumes and T1 measurement were interpreted by an experienced CMR radiologist (JG). T1 measurements for the first 58 subjects were assessed independently by another experienced CMR radiologist (EH) for inter-rater reliability analysis. LGE was assessed independently by both CMR radiologists and cases of disagreement were concluded by consensus. The radiologists were blinded to patient history and reported symptoms, V/Q-scintigraphy results and ISWT scores.

2.8. Statistical analysis

Sample size calculation was performed to ensure sufficient power for the exploration of ECV in participants with and without persistent dyspnea. Normal ECV levels have been measured to be $25 \pm 2.5\%$. [38]. For the power analysis, the minimum ECV difference of clinical interest was set to 3 percent points. With 50 patients in each group, the power for detecting a 3 percent point ECV difference between groups with an α-level of 0.05 was $> 99\%$.

Normal distribution was evaluated by quantile–quantile (QQ) plots and Shapiro-Wilk tests. Continuous variables were reported by means and standard deviations or by medians and interquartile ranges, and compared with Student's *t*-test or Mann-Whitney *U* test as appropriate. Proportions were compared with Fisher's exact test. Confidence intervals of means were calculated from 2000 bootstrap replications.

To evaluate the association of native T1 and ECV with dyspnea and ISWT scores, four separate logistic regression analyses were performed with the parameters T1, ECV, age, sex, BMI, hypertension, mid-wall or coronary pattern LGE, and creatinine forced into the models: 1) Dyspnea vs. native T1, 2) Dyspnea vs. ECV, 3) ISWT vs. native T1 and 4) ISWT vs. ECV. Hypertension was selected as a covariate after analysis of the demographic data due to high prevalence in the population and the tendency of higher prevalence in the dyspneic group, as well as a possible link between hypertension and T1-mapping [39]. To investigate whether any findings were caused by renal insufficiency or heart diseases associated with focal myocardial fibrosis, we performed a sensitivity analysis where patients with eGFR < 60 mL/min/1.73 m^2 or LGE (mid-wall or coronary pattern) were excluded. To explore whether any findings were caused by undiagnosed CTEPH, a sensitivity analysis including only patients without perfusion defects on V/Q-scan was performed. To assess the association between T1-mapping and exercise capacity, patients were classified into two groups: Those who reached

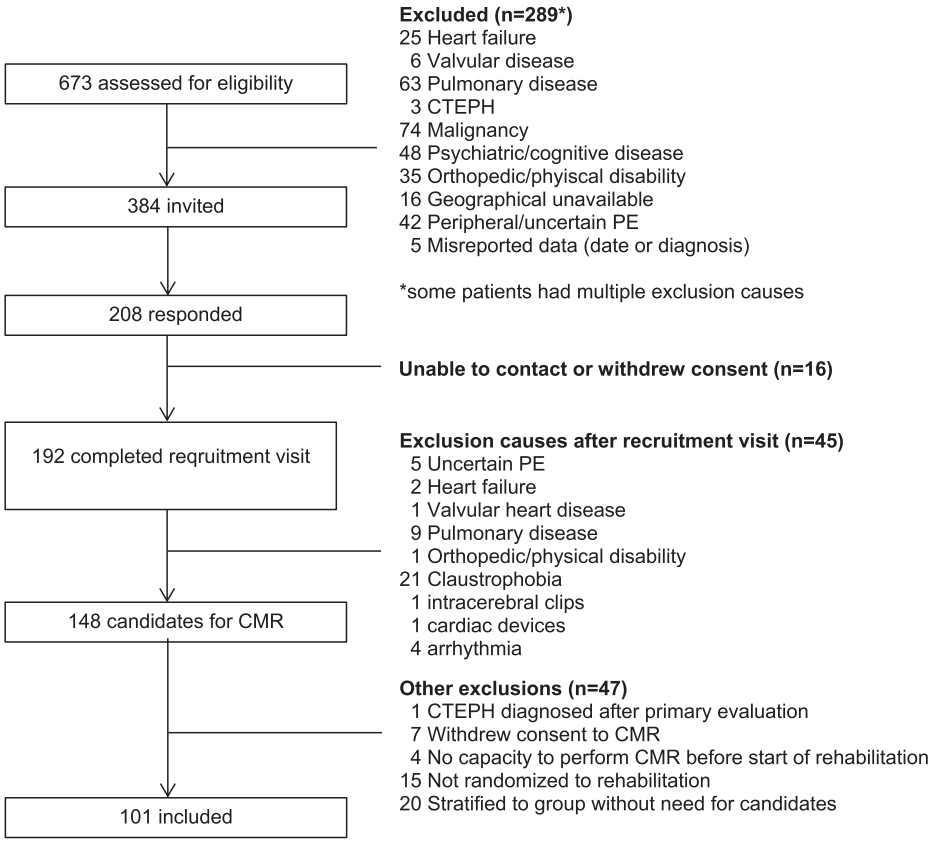

Fig. 1. Inclusion flowchart.

the maximum level on the ISWT (1020 m) and those who did not.

Spearman correlation was performed as appropriate.

Interclass correlation coefficient in a two-level random effects model based on absolute agreement was used to estimate inter-rater reliability for T1 measurements in the first 58 patients.

Odds ratios were reported with 95% confidence intervals. A p-value < 0.05 was considered statically significant. All tests were two-sided. Missing values were not imputed. All statistical analyses were performed using Stata version 16.1 (StataCorp LLC, College Station, TX, USA).

3. Results

Six hundred seventy-three patients were identified from the TROLL registry and assessed for eligibility. Two hundred eighty-nine patients were excluded and 384 patients were invited to participate, of which 208 consented (Fig. 1). An additional 45 patients were excluded after primary evaluation at the reqcruitment visit. Fifty-one patients with persistent dyspnea and 50 patients without dyspnea were consecutively referred to CMR. Inclusion was stopped after achieving the predefined sample size.

Patient characteristics are presented in Table 2. Patients with dyspnea were more frequently female and had higher BMI. There was no difference in age, smoking history or comorbidity between groups. Furthermore, there was no difference in Troponin I or proBNP measured at inclusion time. Mean ISWT score was lower in dyspneic patients compared to non-dyspneic patients: 710 (IQR: 550–930) meters vs. 1020 (IQR: 790–1020) meters, $p < 0.001$. mMRC score was significantly higher in the dyspnea group ($p < 0.001$). Of note, 12 (24%) patients in the non-dyspnea group had mMRC score 1 due to them having symptoms of dyspnea prior to PE but reporting no worsening in symptoms post-PE. Seven non-dyspneic patients (14%) and 11 dyspneic patients (23%) showed perfusion defects at V/Q-scan, however, there was no significant difference between these two groups.

Two patients were referred to right ventricular catheterization after echocardiography-findings at reqcruitment visit consistent with pulmonary hypertension as well as positive V/Q-scintigraphy findings. The final diagnosis of CTEPH was made in one patient: Mean pulmonary artery pressure (mPAP) was 34 mmHg, pulmonary artery wedge pressure (PCWP) was 14 mmHg, and pulmonary vascular resistance (PVR) was 3 Wood. This patient was excluded.

One patient in the dyspnea group fulfilled the echocardiographic criteria for diastolic dysfunction. However, this patient had normal proBNP (141 mg/L), and was retained in the study. Except for mildly reduced right ventricular EF, the CMR volume metrics were normal: LV EF was 56%, LV indexed end diastolic volume was 86 mL/m2, RV EF was 47%, and RV indexed end diastolic volume was 101 mL/m2. LGE was found at the lower right ventricular insertion point. Septal native T1 was 926 ms and ECV was 26%. Native T1 for this patient was 1–2 SD below the mean for non-dyspneic patients. The ECV value was 1–2 SD above the mean.

3.1. CMR findings

Table 3 displays the CMR findings in patients with dyspnea versus patients without dyspnea. Indexed LV mass was lower in dyspneic patients compared to non-dyspneic patients: 51 g/m^2 vs. 55 g/m^2; Odds Ratio 0.96 per g/m^2 (95% CI: 0.92–1.00). No differences were observed between the groups concerning the other volumetric CMR parameters. There were no differences between groups in right or left ventricular strain parameters.

Table 4 and Fig. 2 displays native T1 and ECV metrics. Native T1 was higher in the interventricular septum in dyspneic patients compared to non-dyspneic: 975 vs. 962 ms; difference 13 ms (95% CI: 2–23 ms; $p = 0.02$). ECV was also higher in the interventricular septum: 23.3% vs. 22.3%; difference 0.9 percent points (pp) (95% CI: 0.04–1.8 pp; $p =$

Table 2
Comparison of demographic and clinical data between patients with and without dyspnea, mean (SD) or Median (IQR).

	No dyspnea		Dyspnea		*p*
	(n = 50)		(n = 51)		
Age, years, median (IQR)	61	(55–69)	59	(48–67)	0.08
Male gender, n (%)	39	(78%)	29	(56%)	0.03
Height, cm, mean (SD)	178	(9)	176	(9)	0.38
Weight, kg, mean (SD)	88	(12)	95	(21)	0.15
BMI, kg/m^2, median (SD)	28	(3)	30	(5)	0.02
Current smoker, n (%)	2	(4%)	3	(6%)	0.84
Previous smoker, n (%)	17	(34%)	19	(37%)	
Never smoker, n (%)	31	(62%)	29	(57%)	
ISWT, meters, median (IQR)	1020	(790–1020)	710	(550–930)	<0.001
V/Q-scintigraphy, positive, n (%)	7	(14%)	11	(23%)	0.43
mMRC					
Score 0, n (%)	38	(76%)	0		<0.001
Score 1, n (%)	12	(24%)	36	(69%)	
Score 2, n (%)	0		13	(25%)	
Score 3, n (%)	0		2	(4%)	
Biochemistry at inclusion time					
Troponin I, ng/L					
<5	23	(60%)	16	(40%)	0.22
5–100	10	(26%)	15	(38%)	
>100	5	(13%)	9	(23%)	
proBNP, ng/L, median (IQR)	73	(54–110)[5]	71	(44–104)[5]	0.44
PaO_2, kPa (SD)	11.5	(9.4)[6]	11.2	(1.1)[7]	0.24
Anticoagulation					
Apixaban	11	(22)	16	(31)	0.47
Rivaroxaban	29	(58)	23	(45)	
Warfarin	3	(6)	6	(12)	
Other/combinations	7	(14)	6	(12)	
Ongoing anticoagulation	22	(44)	28	(55)	0.32
Comorbidity					
Diabetes[1], n (%)	0		2	(4%)	0.50
Coronary arterial disease[2], n (%)	1	(2%)	1	(2%)	1.00
Renal insufficiency[3], n (%)	2	(4%)	1	(2%)	0.62
Hypertension[4], n (%)	12	(24%)	22	(42%)	0.06
PE features at time of diagnosis					
Time since PE, years, median (IQR)	1.9	(1.5–3.8)	2.0	(1.3–3.8)	0.94
MBPEC 3–4, n (%)	29	(58%)	33	(65%)	0.54
Right/Left ventricle ratio, median (IQR)	0.94	(0.87–1.04)	0.95	(0.84–1.28)	0.57
PESI-score, median (IQR)	70	(62–77)[8]	67	(54–76)[9]	0.27

[1]Established diagnosis (diet regulated and medicated); [2]Established diagnosis (non-symptomatic); [3]eGFR < 40; [4]Ongoing antihypertensive treatment; [5]n = 46; [6]n = 33; [7]n = 38; [8]n = 49; [9]n = 47.

Abbreviations: IQR – Interquartile Range, ISWT – Incremental Shuttle Walk Test, BMI – Body Mass Index, MBPEC – Mean Bilateral Proximal Extension of the Clot (MBPEC 3–4 represents the combination of central & bilateral PE), PESI – Pulmonary Embolism Severity Index, mMRC – Modified Medical Research Council dyspnea scale; PaO_2 – Arterial Blood Gas/Partial Pressure of Oxygen.

0.04). There was no difference between groups in native T1 or ECV in the left ventricular lateral wall. This association was confirmed in a sensitivity analysis of patients without persistent perfusion defects: The differences in septal native T1 and ECV in patients without perfusion defects were 15 ms (95% CI: 4–26 ms) and 1.4 pp (95% CI: 0.4–2.4 pp), respectively. Septal native T1 was also higher in dyspneic patients compared to non-dyspneic patients when patients with mid-wall and coronary pattern LGE and/or eGFR < 60 mL/min/1.73 m^2 were excluded: 975 vs. 961 ms; difference 14 ms (95% CI: 2–26 ms; p = 0.02). After exclusions of these patients septal ECV was 23.3% vs. 22.3%; difference 1.0 pp (95% CI: 0.0–2.0 pp; p = 0.05).

In the multiple logistic regression analysis, septal native T1 in the interventricular septum had an OR of 1.47 per 10 ms increase (95% CI: 1.10–1.96; p = 0.01) in predicting ISWT scores < 1020 m, but septal native T1 was not associated with PPS. Septal ECV was neither significantly associated with dyspnea nor with ISWT scores < 1020 m (Figure 3–6).

Septal native T1 correlated with ISWT scores (rho = -0.23, p = 0.02) and mMRC scores (rho = 0.28, p = 0.005). Septal ECV correlated with ISWT scores (rho = -0.24, p = 0.02) but not with mMRC scores. Generally, all the significant correlations were weak. There were no correlations between native T1 and ECV versus proBNP, Troponin I or PaO_2.

There were no differences in native T1, ECV, CMR volumetric parameters, proBNP and Troponin I between patients with or without LGE at right ventricular insertion points.

The T1 measurement inter-rater correlation was 0.89 (95% CI: 0.86–0.93) in pre contrast myocardial T1 measurements and 0.71 (95% CI: 0.60–0.79) post contrast myocardial T1 measurements.

4. Discussion

In this study, we explored possible associations between T1 mapping parameters and persistent dyspnea in patients with a history of PE. We found higher myocardial native T1 in the interventricular septum in both dyspneic patients compared to non-dyspneic, and in patients with reduced exercise capacity (ISWT scores < 1020). The association between native T1 and exercise capacity was found to be independent of gender, age and BMI in a multivariable analysis. Further, ECV was higher in the interventricular septum in patients with dyspnea and in patients with ISWT scores < 1020. However, this association was not found in the multivariable analysis.

Several studies have shown myocardial fibrosis in CTEPH [28,40,41]. To our knowledge, T1 mapping parameters have not been previously reported in non-CTEPH patients with persistent dyspnea after PE. Of note, the differences in native T1 in our study seem to be smaller

Table 3
Comparison of indexed cardiac volumes and late gadolinium enhancement in patients with and without dyspnea, mean (SD) with crude Odds Ratio (95% CI).

	No dyspnea		Dyspnea		Crude
	(n = 50)		(n = 51)		Odds Ratio
Left ventricle					
Ejection fraction, %	53	(7)	51	(7)	0.96 (0.91 – 1.02)
End diastolic volume, mL/m^2	81	(18)	76	(14)	0.98 (0.96 – 1.01)
End systolic volume, mL/m^2	38	(11)	37	(8)	0.99 (0.95 – 1.03)
Stroke volume, mL/m^2	43	(10)	39	(9)	0.96 (0.92 – 1.00)
Mass, g/m^2	55	(26)	51	(28)	0.96 (0.91 – 1.00) *
Global longitudinal strain	−16	(3)	−16	(3)	0.99 (0.88 – 1.12)
Global circumferential strain	−18	(2)	−18	(3)	1.10 (0.95 – 1.28)
Right ventricle					
Ejection fraction, %	46	(8)	45	(7)	0.97 (0.92 – 1.02)
End diastolic volume, mL/m^2	90	(18)	87	(17)	0.99 (0.97 – 1.01)
End systolic volume, mL/m^2	49	(12)	48	(10)	1.00 (0.96 – 1.03)
Stroke volume, mL/m^2	42	(11)	39	(9)	0.97 (0.93 – 1.01)
Global longitudinal strain	−17	(4)	−18	(3)	0.93 (0.83 – 1.04)
Lateral strain	–23	(4)	−24	(4)	0.94 (0.85 – 1.03)
Global circumferential strain	−11	(3)	−10	(3)	1.02 (0.90 – 1.15)
Left atrium[1]					
Maximum volume, mL/m^2	37	(14)	35	(12)	0.99 (0.96 – 1.02)
Right atrium[2]					
Maximum volume, mL/m^2	39	(13)	38	(15)	0.99 (0.97 – 1.02)
Late gadolinium enhancement					
Right Ventricular Insertion Point, n (%)	11	(22%)	19	(37%)	2.11 (0.88 – 5.06)
Midwall, n (%)	5	(10%)	2	(4%)	0.37 (0.07 – 1.99)
Coronary pattern, n (%)	1	(2%)	3	(6%)	3.06 (0.31 – 30.48)

[1]Biplane area length method; [2]Single plane area length method.
* Significant at the 0.05 level.

than what has been reported for patients with CTEPH. One possible explanation to our finding is that diffuse myocardial fibrosis also occurs in non-CTEPH patients with dyspnea after PE, but to a smaller extent than in CTEPH. Although we have done our best to exclude CTEPH-patients, it could be argued that our findings could be explained by the inclusion of patients with undiagnosed CTEPH. In an attempt to explore this possibility, we analyzed T1 and ECV in a subgroup of patients with normal V/Q-scintigraphy. The differences in T1 and ECV between dyspneic and non-dyspneic patients were still significant in the subgroup analysis, which indicates that it is unlikely that our results can be explained by undiagnosed CTEPH.

We wish to emphasize that increased native T1 and ECV are not disease-specific entities, but should be interpreted as unspecific markers of myocardial remodeling/fibrosis and are found in conditions such as CAD, hypertension, amyloidosis, renal insufficiency and myocarditis. Further, an increase in native T1 or ECV is not specific for diffuse myocardial fibrosis, but can also be detected in other appearances of increased interstitial volume, e.g. acute or chronic edema. It is therefore not possible to make firm conclusions on causal relationships in this study. Thus our finding of increased native T1 and ECV in patients with dyspnea after PE should be considered as hypothesis generating. Further studies are required to evaluate native T1 and ECV to confirm the potential role of myocardial fibrosis in the etiology of Post Pulmonary Embolism Syndrome (PPS).

The magnitude of native T1 and ECV differences was modest and within 1 SD with a considerable overlap between the groups. The difference in ECV was less than the predefined minimum difference of clinical interest and the mean in both groups were probably within the normal range. Although we have found statistically significant differences, it must be emphasized that it is not possible to conclude whether the differences are clinically significant.

Dyspnea is associated with coronary artery disease (CAD). Since patients with CAD were not excluded from the study, it could be argued that our findings may be related to the inclusion of such patients. However, it is rare that dyspnea is the only present symptom in patients with CAD. Additionally, there were no differences between dyspneic and non-dyspneic patients with regard to cardiac biomarkers. Although increased native T1 and ECV have been detected in CAD [42,43], CAD is associated with focal rather than diffuse fibrosis. Furthermore, our findings were confirmed in a sensitivity analysis where patients with LGE were excluded. As such, we consider it unlikely that our results could be explained by undiagnosed CAD.

We found no significant difference in right ventricular insertion point late gadolinium enhancement in dyspneic patients compared to non-dyspneic patients. Furthermore, we found no differences in CMR derived volumes, ISWT scores, mMRC scores, proBNP, proBNP or Troponin I in patients with right ventricular insertion point enhancement compared to those without. This is in contrast to previous findings in patients with CTEPH, where right ventricular EF is decreased in patients with right ventricular insertion point LGE [28]. There may be a reasonable possibility that the study is underpowered to be able to detect a difference in right ventricular insertion point LGE, but it must also be mentioned that such enhancement is an unspecific finding and frequently detected in normal hearts [44].

5. Limitations

This was a cross sectional, single center study with a limited number of patients. We did not perform cardiopulmonary exercise test or right ventricular catheterization (except when it was clinically indicated) which would have allowed for a stronger conclusion with regard to the relevance of the observed increased native T1 and ECV in the patients with dyspnea after PE. Also, although patients with established CTEPH, chronic obstructive pulmonary disease and/or heart failure diagnoses were excluded from the study, we cannot rule out the possibility that some of the included patients had undiagnosed cardiopulmonary conditions, such as amyloidosis or sequela of myocarditis. However, we have no indication that myocardial changes were present before the PE

Table 4
Comparison of myocardial native T1 and extracellular volume fraction (ECV) between patients with and without dyspnea and between, and between patients who reached the maximum ISWT of 1020 m and patients with ISWT<1020 m. Means (SD) and difference of mean (95% CI).

	Non– dyspneic		Dyspneic		Difference		ISWT = 1020		ISWT < 1020		Difference	
	(n = 50)		(n = 51)				(n = 36)		(n = 64)			
Native T1												
Septum, ms	962	(28)	975	(24)[1]	13	(2 – 23) *	960	(24)	975	(27)	15	(5 – 25) ***
Lateral Wall, ms	956	(28)	966	(27)[1]	9	(-1 – 21)	952	(21)	966	(30)	14	(4 – 24) ***
ECV												
Septum, %	22.3	(2.2)	23.3	(2.5)[2]	0.9	(0.04 – 1.8) *	22.5	(2.4)	22.9	(2.3)[3]	0.4	(-0.5 – 1.4)
Lateral Wall, %	21.7	(1.8)	22.0	(2.5)[1]	0.4	(-0.4 –1.3)	21.3	(1.8)	22.1	(2.4)	0.8	(0.0 – 1.6)

*Significant at the 0.05 level; ** Significant at the 0.01 level *** 0.005.
[1]n = 50; [2]n = 49; [3]n = 63; [4]n = 64.

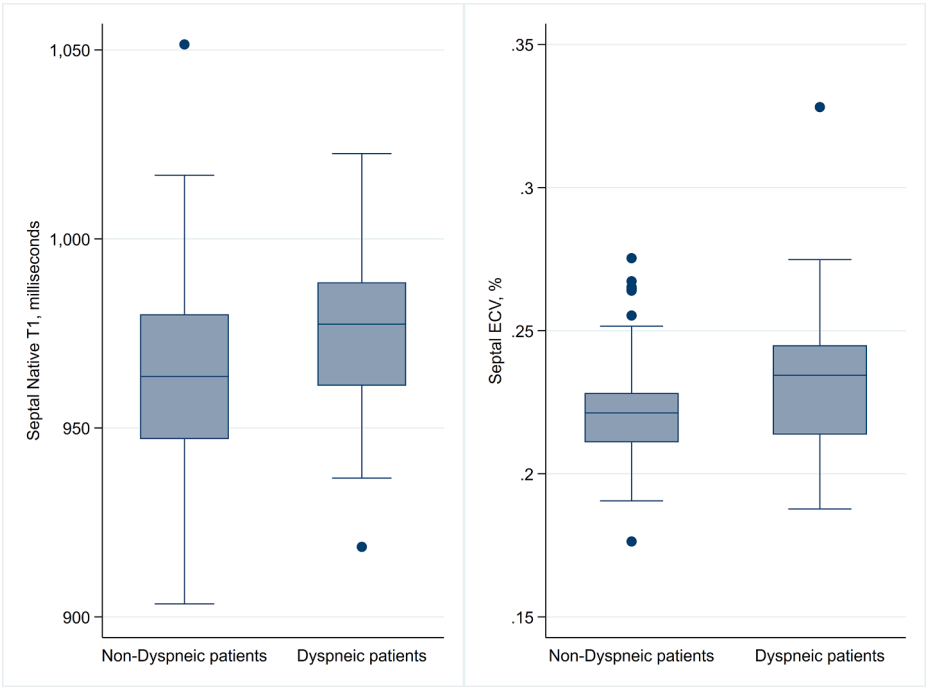

Fig. 2. Septal native T1 and ECV in dyspneic patients compared with non-dyspneic.

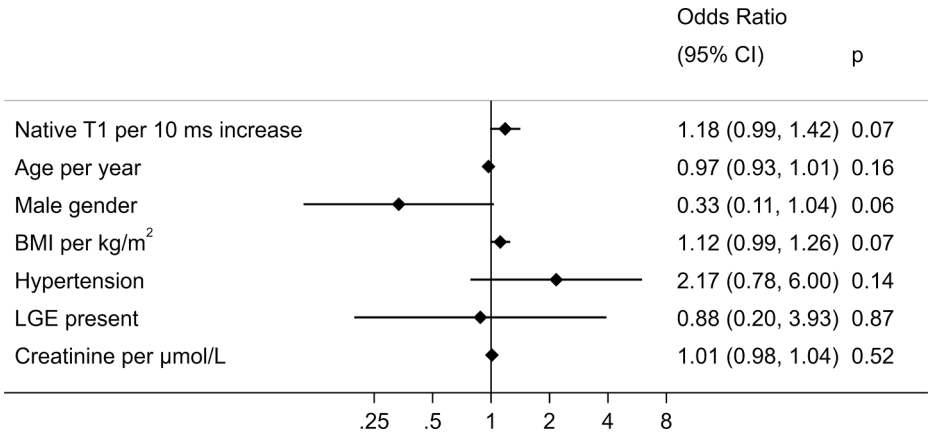

Fig. 3. Results of a multiple logistic regression analysis where septal native T1 is evaluated as a predictor of dyspnea that emerged after pulmonary embolism. Abbreviations: BMI – Body Mass Index, LGE – Late Gadolinium Enhancement (mid-wall or coronary pattern).

event in the included patients.

We did not perform stress perfusion CMR or other imaging to exclude CAD. The results from such tests could have allowed a more reliable assessment of the prevalence of CAD in the cohort.

Patients were dichotomously classified as dyspneic or non-dyspneic based on interviews and a self-completed questionnaire. It must be emphasized that dyspnea is strongly patient-dependent. Further, we included patients up to 6 years after the episode of pulmonary embolism.

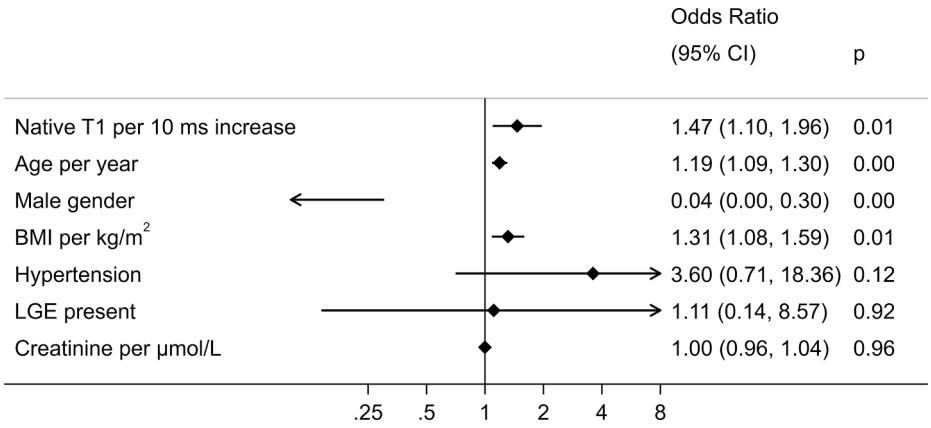

Fig. 4. Results of a multiple logistic regression analysis where septal native T1 is evaluated as a predictor of reduced exercise capacity defined as Incremental Shuttle Walk Test score below 1020 m. Abbreviations: BMI – Body Mass Index, LGE – Late Gadolinium Enhancement (mid-wall or coronary pattern).

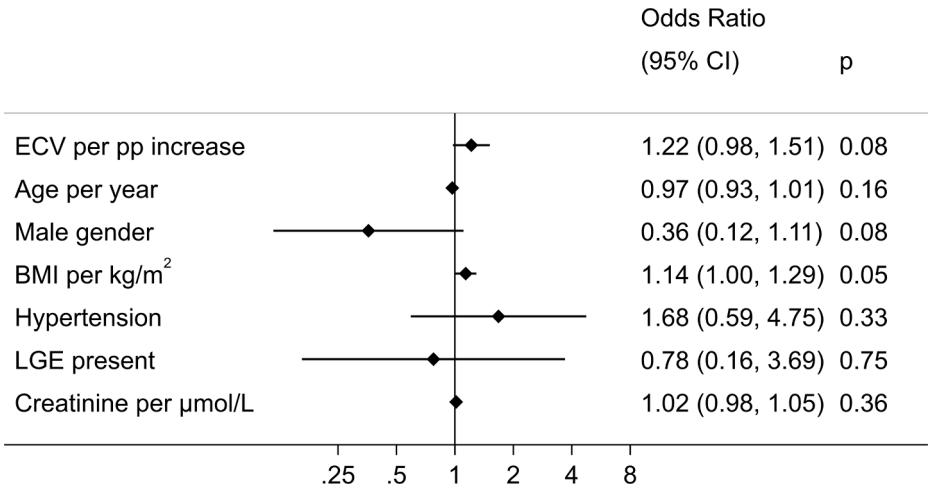

Fig. 5. Results of a multiple logistic regression analysis where septal extracellular volume (ECV) is evaluated as a predictor of dyspnea that emerged after pulmonary embolism. Abbreviations: BMI – Body Mass Index, LGE – Late Gadolinium Enhancement (mid-wall or coronary pattern).

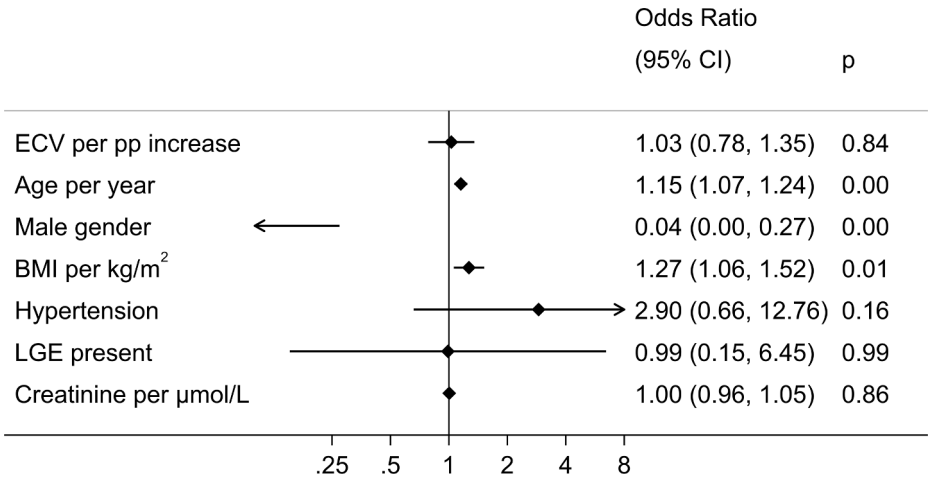

Fig. 6. Results of a multiple logistic regression analysis where septal extracellular volume (ECV) is evaluated as a predictor of reduced exercise capacity defined as Incremental Shuttle Walk Test score below 1020 m. Abbreviations: BMI – Body Mass Index, LGE – Late Gadolinium Enhancement (mid-wall or coronary pattern).

For some patients it was difficult to be certain whether the dyspnea had occurred after PE. The classification in dyspneic or non-dyspneic was prone to information/recall bias which may have affected the results.

Lastly, we only compared patients with a history of PE who had persistent dyspnea to those who were fully recovered. Since we did not include healthy subjects, we cannot comment on deviations from normal native T1, ECV or other cardiac indices.

6. Conclusion

Native T1 and ECV were higher in patients with persistent dyspnea after PE compared to non-dyspneic patients. This indicates that myocardial fibrosis might be involved the development of dyspnea after PE. However, the difference between dyspneic and non-dyspneic patients was modest and further studies are required to validate our findings and to determine clinical relevance.

Authorship Details

J. Gleditsch, Ø. Jervan, W. Ghanima and E. Hopp were responsible for the design of the study. Ø. Jervan was responsible for inclusion of subjects, spirometry and echocardiography. J. Gleditsch was responsible for CMR and CTA image interpretation. The statistical analyses were performed by J. Gleditsch with contribution by R. Holst. J. Gleditsch drafted the first manuscript. All authors contributed to the interpretation of the results and revision of the manuscript. All authors have read and approved the final version of the manuscript. All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [W. Ghanima reports personal fees for lectures and participation in advisory board from Novartis, Amgen, Grifols, SOBI, UCB, ARGENX, Sanofi, Principia biophrma, Pfizer, BMS and Bayer and grants from Bayer and, PfizerBMS, all outside the submitted work. Dr. FA Klok reports research support from Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Daiichi-Sankyo, Actelion, the Dutch thrombosis association, The Netherlands Organization for Health Research and Development and the Dutch Heart foundation. J. Gleditsch, Ø. Jervan, M. Tavoly, O. Geier, R. Holst and E. Hopp report no relationships that could be construed as a conflict of interest. The project received an unrestricted grant from the Norwegian patient organizations “Fredrikstad Tuberkuloseforenings Stiftelse” and “Landsforeningen for hjerte- og lungesyke”.].

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