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ABSTRACT

Introduction: Application of the chronic thromboembolic pulmonary hypertension (CTEPH) rule out criteria (manual electrocardiogram [ECG] reading and N-terminal pro-brain natriuretic peptide [NTproBNP] test) can rule out CTEPH in pulmonary embolism (PE) patients with persistent dyspnea (InShape II algorithm). Increased pulmonary pressure may also be identified using automated ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO).

Method: A predefined analysis of the InShape II study was performed. The diagnostic performance of the VG-RVPO for the detection of CTEPH and the incremental diagnostic value of the VG-RVPO as new rule-out criteria in the InShape II algorithm were evaluated.

Results: 60 patients were included; 5 (8.3%) were ultimately diagnosed with CTEPH. The mean baseline VG-RVPO (at time of PE diagnosis) was −18.12 mV·ms for CTEPH patients and − 21.57 mV·ms for non-CTEPH patients (mean difference 3.46 mV·ms [95%CI −29.03 to 35.94]). The VG-RVPO (after 3–6 months follow-up) normalized in patients with and without CTEPH, without a clear between-group difference (mean Δ VG-RVPO of −8.68 and − 8.42 mV·ms respectively; mean difference of −0.25 mV·ms, [95%CI −12.94 to 12.44]). The overall predictive accuracy of baseline VG-RVPO, follow-up RVPO and Δ VG-RVPO for CTEPH was moderate to poor (ROC AUC 0.611, 0.514 and 0.539, respectively). Up to 76% of the required echocardiograms could have been avoided with VG-RVPO criteria replacing the InShape II rule-out criteria, however at cost of missing up to 80% of the CTEPH diagnoses.

Conclusion: We could not demonstrate (additional) diagnostic value of VG-RVPO as standalone test or as on top of the InShape II algorithm.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is the most feared long-term complication of acute pulmonary embolism (PE) [1–4]. CTEPH can be fatal unless it is timely diagnosed and treated adequately [1–3,5,6]. Therefore, diagnosing CTEPH early after PE is key [7]. This latter remains a challenge with a diagnostic delays reported up to 24 months because of the non-specific clinical presentation of CTEPH, high frequency of post-pulmonary embolism functional limitations, low awareness among physicians and inefficient use of healthcare resources in the follow-up of PE patients [8–11]. Over the last years there has been no improvement of this diagnostic delay (median of 14.1 months from time of onset of symptoms till diagnosis in 2007–2009 vs 15 months in 2015–2018 [8,12]), underlining the need for dedicated, straightforward PE follow-up algorithms to detect CTEPH.

Currently there are multiple strategies for early CTEPH detection in PE patients. The European Society of Cardiology (ESC) Guideline on PE recommends echocardiography as a first step in patients with persisting dyspnea, functional limitations or risk factors for CTEPH [13]. For patients with high probability of pulmonary hypertension or intermediate probability of pulmonary hypertension on echocardiogram in combination with elevated N-terminal pro-brain natriuretic peptide (NTproBNP) levels or relevant risk factors, further diagnostic testing is indicated by ventilation/perfusion lung scintigraphy and right heart catheterization. A low probability of pulmonary hypertension on echocardiography rules out CTEPH. An alternative strategy involves sequential application of the CTEPH prediction score and CTEPH-rule out criteria to identify patients with an indication for echocardiography, i.e. the InShape II follow-up algorithm [14–16]. The CTEPH-rule out criteria involve manual electrocardiogram (ECG) reading and a NTproBNP blood test [16–18]. Normal NTproBNP and no ECG specific signs for right ventricle overload (defined as: [1] rSR' or rSr' pattern in lead V1, [2] R:S $>$ 1 in lead V1 with $R > 0.5$ mV or [3] QRS axis $> 90°$) rules out CTEPH, otherwise echocardiography is needed to further evaluate the presence of CTEPH. This algorithm has been proven safe and efficient with an indication for echocardiography in only 19% of patients, at cost of a diagnostic failure rate of 0.29% [14].

Increased pulmonary pressure may also be identified using ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) [19–21]. In a normal heart the ventricular gradient points in a left direction, therefore a normal VG-RVPO is negative. With increase of right ventricle pressure, the VG-RVPO becomes more positive and can therefore detect right ventricle pressure overload (Fig. 1). Since the VG-RVPO is a numerical value that can be dichotomized to absent or present signs of right ventricle pressure overload with previous derived cut-off values, the VG-RVPO might be more accurate than manual ECG reading for the assessment of increased right ventricle pressure on ECG [22–25]. Therefore, we hypothesized that replacing manual ECG reading with automated vector ECG assessment can be used to improve the accuracy of the InShape II follow-up algorithm. In a predefined analysis of the InShape II study, we investigated the diagnostic accuracy of the VG-RVPO for the detection of CTEPH and the incremental diagnostic value of the VG-RVPO to the InShape II algorithm [14].

Methods

Patients and study design

This was a predefined secondary outcome of the InShape II study which was a prospective international multicenter management study of patients diagnosed with an acute PE between February 2016 and October 2017. The study design, inclusion and exclusion criteria and outcome measures have been published earlier [14]. In short, patients were categorized as high or low risk of developing CTEPH based on the CTEPH prediction score. During the 3–6 month follow-up, patients at high risk of CTEPH or with persistent symptoms were subjected to the CTEPH rule-out criteria. If a patient had a normal NTproBNP and no ECG signs of right ventricle pressure overload, CTEPH was considered ruled out i.e. echocardiogram deemed unnecessary. If a patient had an abnormal NTproBNP or ECG signs of right ventricle pressure overload, an echocardiogram was performed according to the 2015 ESC/ERS guidelines on PH [26]. If the echocardiogram showed low probability of PH, CTEPH was considered to be ruled out. Patients with an intermediate or high probability of pulmonary hypertension on echocardiogram were referred to a CTEPH expertise center for a diagnostic workup of suspected CTEPH. All study patients received an echocardiogram at 2 years of follow-up. The primary outcome of the InShape II study was to determine the failure rate of the screening algorithm, which was defined as the 2-year incidence of confirmed CTEPH in patients with PE in whom echocardiogram was deemed unnecessary by the algorithm.

The current study included all patients from the InShape II study with an indication for applying the rule-out criteria according to the algorithm, in whom a baseline ECG at the moment of the acute PE diagnosis could also be retrieved. Patients were excluded from the current analysis if (1) the baseline ECG and the acute PE event were $>$ 14 days apart, (2) the follow-up ECG and the follow-up moment at the outpatient clinic (3–6 months after the acute PE event) were $>$ 3 months apart, or (3) the original digital recording of the ECG was not stored. We did not include patients in whom CTEPH was considered ruled out based on a low prediction score and no CTEPH specific symptoms (i.e. patients without an indication for application of the rule-out criteria), since

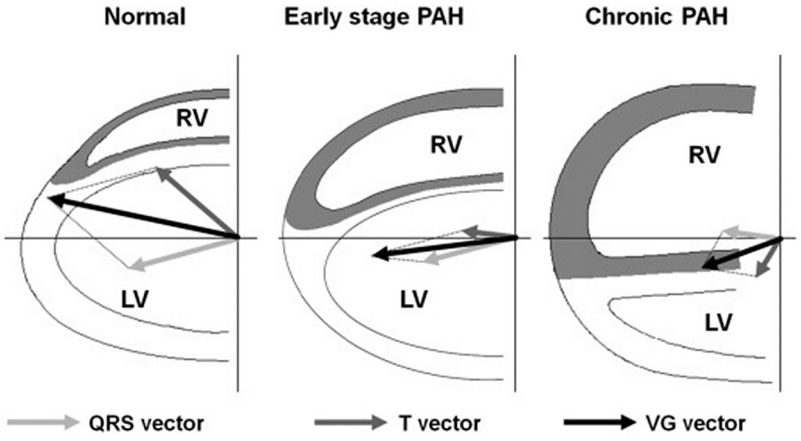

Fig. 1. Change in cardiac vectors from the normal physiologic situation to respectively early stage and chronic PH. Reprinted from Couperus et al. with permission [24]. Pulmonary arterial hypertension PAH.

replacement of manual ECG reading with the VG-RVPO would not have resulted in a different outcome in these patients.

Study objectives

The main aim of this study was to investigate the diagnostic accuracy of the VG-RVPO for the detection of CTEPH in a population of PE patients with a high a-priori probability of CTEPH. Other objectives were to assess the optimal cut-off value of VG-RVPO for detecting CTEPH and to determine the additional diagnostic value of the VG-RVPO to the InShape II algorithm i.e. whether changing the rule-out criteria (manual ECG reading plus NT-proBNP measurement) to rule out criteria based on the VG-RVPO (±NT-proBNP measurement) would allow for more efficient selection of patients in whom CTEPH can be ruled out without the need for echocardiography.

ECG measurements

ECGs were standard 10-s 12 lead ECGs recorded in supine position (25 mm/s). To determine the ECG variables, the dedicated Leiden ECG analysis and decomposition software program (LEADS) was used [27]. An independent investigator performed all LEADS analyses, blinded to the patients characteristics and outcome. The LEADS software computed multiple vector-cardiogram (VCG) values of which the ventricular gradient (VG) is most important for this study. The VG is defined as the 3D integral of the heart vector over the QT interval. Therefore, the VG is an indicator for how the action potential morphology is distributed over the heart [28]. For detection of right ventricular pressure overload previous research has shown that the projection in the 155° azimuth and 27° elevation direction is the most optimal, since this projection is directed over the right ventricle [19,20,22–24]. This projection is called the VG-RVPO (ventricular gradient – optimized for right ventricular pressure overload). Since in a normal heart the VG points in a left direction, a normal VG-RVPO is negative and with increase of right ventricular pressure the VG-RVPO becomes more positive.

Study definitions

CTEPH was diagnosed if the following diagnostic criteria were met after ≥3 months of adequate therapeutic anticoagulation according to the relevant guidelines at the moment of the study initiation: (1) ≥1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning; (2) mean pulmonary artery pressure ≥ 25 mmHg at rest measured by invasive right heart catheterization; (3) pulmonary artery wedge pressure ≤ 15 mmHg [26]. All diagnoses of CTEPH were assessed in a recognized CTEPH expertise center.

The baseline VG-RVPO was derived from the ECG made at time of acute PE diagnosis (±14 days; [mV · ms]). The follow-up VG-RVPO was derived from the ECG that was made at the follow-up moment 3–6 months after the acute PE diagnosis, at which the CTEPH rule-out criteria were applied (±91 days; [mV · ms]). Δ VG-RVPO was defined as the difference between follow-up VG-RVPO and baseline VG-RVPO (mV · ms).

The (baseline or follow-up) VG-RVPO cut-off point for the detection of pulmonary hypertension derived from previous studies is <−13 mV · ms. [22–25] This means a VG-RVPO <-13 mV · ms was considered normal (pulmonary hypertension ruled out) and a VG-RVPO of ≥ −13 mV · ms was considered abnormal (possible pulmonary hypertension), although different cut-off points have been evaluated in this study.

Statistical analysis

Normally distributed continuous data were described as a mean (±standard deviation [SD]) and compared using an independent *t*-test. Abnormally distributed continuous data were described as a median (interquartile range [IQR]). Categorical variables were described as numbers (percentage).

For the analysis of diagnostic accuracy of the VG-RVPO for the detection of CTEPH, sensitivity and specificity of the VG-RVPO with confidence interval (95%CI) were calculated. Moreover, ROC curves were plotted, the area under the curve (AUC) with 95%CI was assessed and odds ratios (ORs) were calculated and depicted with a 95%CI.

For the selection of optimal cut-off points for baseline, follow-up and Δ VG-RVPO, cut-off points with the highest Youden-index have been evaluated [30].

Finally, hypothetical scenarios of application of the InShape II algorithm with new rule-out criteria based on the VG-RVPO have been evaluated. These scenarios are combinations of the previously described cut-off values with a NTproBNP measurement. Moreover, based on the VG-RVPO values of the CTEPH cases, a scenario with other cut-off values has also been selected to diagnose all CTEPH cases and avoid most echocardiograms. Statistical analysis was performed using SPSS version 25.0 (IBM, Chicago, Illinois).

Results

Study population

Out of the 424 patients included in the InShape II study, 222 had an indication for application of the rule-out criteria according to the InShape II algorithm of which a total of 60 patients were included in this study after applying in- and exclusion criteria (**supplementary data *fig. S1***). The baseline characteristics of the study patients are described in Table *1*; 50.0% was male, the mean age was 60 (SD 15) years, the median time between the PE event and the follow-up date was four months

Table 1
Baseline characteristics of the included patients. All patients (n = 60).

Age (years, mean ± SD)	60 (15)
Male gender (n, %)	30 (50.0)
BMI (kg/m^2, median, IQR)	27.8 (24.5–30.3)
Unprovoked PE (n, %)	44 (73.3)
Previous VTE (n, %)	12 (20.0)
right ventricle/left ventricle ratio > 1 on CT (n, %)	26 (43.3)
Comorbidities (n, %)	
Anaemia	5 (8.3)
COPD/asthma	5 (8.3)
Active malignancy	5 (8.3)
Diabetes mellitus	0 (0)
Coronary artery disease	3 (5.0)
Rheumatic disease	5 (8.3)
Hypothyroidism	4 (6.7)
Interstitial lung disease	0 (0)
Inflammatory bowel disease	2 (3.3)
Known antiphospholipid antibodies	1 (1.7)
Major vasculitis syndromes	0 (0)
Prior infected pacemaker leads	0 (0)
Splenectomy	0 (0)
Anticoagulant treatment at 3 month follow-up visit (n, %)	
DOAC	35 (58.3)
VKA	22 (36.7)
LMWH	4 (6.7)
Time between PE primary event and follow-up date (months, median, IQR)	4 (3–6)
Mean time between baseline ECG and follow-up ECG (months, median, IQR)	4 (2–6)

Active malignancy was defined as diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months or recurrent metastatic cancer. Rheumatic disease was defined as known rheumatic arthritis, osteoarthritis, connective tissue disease, systemic lupus erythematosus, ankylosing spondylitis or Sjögren syndrome. Anaemia was defined as: males < 8.5 mmol/L or < 13.5 g/Dl; females < 7.5 mmol/L or < 12.0 g/dL.
BMI, body mass index; DOAC direct oral anticoagulant; LMWH, low-molecular weight heparin; PE pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

(IQR 3–6) and five patients (8.3%) were diagnosed with CTEPH.

VG-RVPO results

Table 2 presents the VG-RVPO measurements in the study patients. For patients with CTEPH the mean baseline VG-RVPO was −18.12 mV · ms and for patients without CTEPH this was −21.58 mV · ms (mean difference 3.46 mV · ms [95%CI −29.03 to 35.94]). For patients with CTEPH the mean follow-up VG-RVPO was −26.80 mV · ms and for patients without CTEPH this was −30.00 mV · ms (mean difference 3.20 mV · ms [95%CI −13.05 to 19.46]). The mean Δ VG-RVPO therefore was −8.68 mV · ms for CTEPH patients and − 8.42 mV · ms for patients without CTEPH (mean difference − 0.25 mV · ms [95%CI −12.94 to 12.44]).

Baseline VG-RVPO with a cut-off point of <−13 mV · ms had a sensitivity of 40% (95%CI 5.3–85) and a specificity of 73% (95%CI 59–84). Follow-up VG-RVPO with a cut-off point of <−13 mV · ms had a sensitivity of 20% (95%CI 0.51–72) and a specificity of 80% (95%CI 67–90). Most patients (39/60; 65%) had a normal VG-RVPO of <−13 mV · ms at baseline which remained normal during follow up. There was no association between CTEPH and an abnormal baseline VG-RVPO (OR 1.8 [95%CI 0.27–12] cut-off point of <−13 mV · ms) or abnormal follow-up VG-RVPO (OR 1.0 [95%CI 0.10–9.9] cut-off point of <−13 mV · ms).

The overall predictive accuracy of baseline VG-RVPO, follow-up RVPO and Δ VG-RVPO for detection of CTEPH was moderate to poor, with an AUC of the ROC of 0.615 (95%CI 0.286–0.943), 0.520 (95%CI 0.252–0.788) and 0.538 (95%CI 0.207–0.869), respectively.

Evaluating different VG-RVPO cut-off values

Based on the highest Youden-Index the best cut-off value for baseline VG-RVPO is <2 mV · ms (sensitivity 40% [95%CI 5.3–85]; specificity 96% [95%CI 87–100]), <−3 mV · ms for follow-up VG-RVPO (sensitivity 20% [95%CI 0.51–72]; specificity 95% [95%CI 85–99]) and < 5 mV · ms for ΔVG-RVPO (sensitivity 40% [95%CI 5.3–85]; specificity 87% [76–95]). (**Supplementary data table S2** and **table S3**). There was an association between CTEPH and a baseline VG-RVPO with a cut-off value of <2 mV · ms (OR 17.7 [95%CI 1.8–173). There was no association between CTEPH and an abnormal follow-up VG-RVPO with a cut-off value of <−3 mV · ms (OR 4.3 [95%CI 0.36–52]) or abnormal ΔVG-RVPO with a cut-off point of <5 mV · ms (OR 4.6 [95%CI 0.65–32]). We were unable to identify thresholds with a relevant higher sensitivity and specificity ratio.

Changing rule-out criteria based on VG-RVPO

Application of the InShape II rule-out criteria (normal NTproBNP and no ECG signs of RV overload) in our study population would have resulted in diagnosis of all CTEPH cases ($n = 5$) and need for 21 echocardiograms. For different VG-RVPO rule-out criteria with different cut-off values, the hypothetical number of echocardiograms prevented compared to application of the rule-out criteria of the original InShape II algorithm and the proportion of missed CTEPH diagnoses were evaluated (Table 3).

Three of the strategies with rule-out criteria based on the previously described cut-off values failed to decrease the number of echocardiograms needed and missed 20–40% of the CTEPH diagnoses (Table 3; **scenario B, C, and G**). In three strategies the number of echocardiograms needed would be reduced with 29–76% at the cost of 20–80% missed CTEPH diagnoses (Table 3**; strategy D, E and F**). A scenario in which CTEPH would be considered ruled-out based on a combination of normal baseline VG-RVPO of <2 mV · ms, follow-up VG-RVPO <-3 mV · ms and Δ VG-RVPO of <5 mV · ms in combination with normal NTproBNP measurement would have resulted in diagnosis of all CTEPH cases, but would have increased the need for echocardiography with 9.5%(Table 3**; option H**).

To select a scenario in which most echocardiograms were avoided without missing CTEPH diagnosis, cut-off values were selected based on the VG-RVPO values of CTEPH cases with a normal NTproBNP during follow-up (**supplementary data table S1**). In this scenario CTEPH was considered ruled out based on a baseline VG-RVPO <5 mV · ms, follow-up VG-RVPO of <0 mV · ms, ΔVG-RVPO of <13 mV · ms and normal NTproBNP. All CTEPH patients would have been detected and a limited number of 2 echocardiograms would have been prevented (−9.5% of all echocardiograms) (Table 3**; strategy I).**

Discussion

This predefined analysis of the InShape II study showed limited additional value of VG-RVPO as standalone test for the detection of CTEPH after acute PE and as a component within the InShape II algorithm. We observed the expected VG-RVPO improvement over time after acute PE, but the extent of improvement did not differentiate CTEPH from non-CTEPH patients.

We had anticipated a better diagnostic value of VG-RVPO for the detection of CTEPH than observed based on previous literature. The VG is a vectorial measurement over the QRS complex and T-wave. Chronic increased right ventricle pressure load will lead to changed action potential duration resulting in a VG change [21]. Therefore, a change in magnitude and/or orientation of the VG represents a change in right ventricle pressure load [21,28]. Previous research confirmed the diagnostic value of the VG. The VG magnitude projected over the x-axis (VG-X) has shown an improved diagnostic accuracy of chronic right ventricle pressure overload for the detection of pulmonary arterial hypertension patients compared to conventional ECG parameters (rSR' or rSr' in V1, R:S > 1 with $R > 0.5$ mV in V1, and QRS axis > 90°) [21]. Also, the VG-RVPO significantly correlates with mean pulmonary artery pressure in

Table 2
VG-RVPO measurements in the study patients.

ECG parameters	All patients (n = 60)	No CTEPH ($n = 55$)	CTEPH ($n = 5$)	Mean difference (95%CI)
VG-RVPO at baseline (mV . ms), mean ± SD	−21.28 ± 14.70	−21.58 ± 13.56	−18.12 ± 26.33	3.46 (−29.03 to 35.94)
VG-RVPO during follow-up (mV . ms), mean ± SD	−29.73 ± 17.26	−30.00 ± 17.41	−26.80 ± 17.00	3.20 (−13.05 to 19.46)
Δ VG-RVPO (mV . ms), mean ± SD	−8.45 ± 13.46	−8.42 ± 12.76	−8.68 ± 21.70	−0.25 (−12.94 to 12.44)
Change in VG-RVPO, n (%)[a]				
Normal-normal	39 (65.0)	36 (65.5)	3 (60.0)	
Abnormal-abnormal	8 (13.3)	7 (12.7)	1 (20.0)	
Aabnormal-normal	9 (15.0)	8 (14.5)	1 (20.0)	
Normal-abnormal	4 (6.7)	4 (7.3)	0 (0.0)	

[a] [baseline VG-RVPO]-[follow-up VG-RVPO]. The cut-off value for a normal value of the VG-RVPO set at − 13 mV ms, with < −13 mV ms being considered normal and ≥ −13 mV ms as abnormal. CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; VG-RVPO ventricular gradient optimized for right ventricular pressure overload.

Table 3
results of change in rule-out criteria.

Rule out criteria (cut-off value^)	Patients with an echocardiography indication because rule-out criteria are not met			Patients where CTEPH is considered ruled out without the need for echocardiography because rule-out criteria are met		
	CTEPH n (% of all CTEPH diagnosis)	No CTEPH, n	Total, n (% difference with InShape II[α])	CTEPH, n (% of all CTEPH diagnosis)[β]	No CTEPH, n	Total, n
A: No ECG abnormalities plus normal NTproBNP (InShape II)	5 (100.0)	16	21 (n.a.)	0 (0.0)	39	39
B: normal baseline VG-RVPO (<−13) plus normal NTproBNP	4 (80.0)	20	24 (+14.3)	1 (20.0)	35	36
C: normal follow-up VG-RVPO (<−13) plus normal NTproBNP	3 (60.0)	18	21 (±0.0)	2 (40.0)	37	39
D: No ECG abnormalities plus normal NTproBNP and normal follow up VG-RVPO (<−13)*	1 (20.0)	4	5 (−76.2)	4 (80.0)	51	55
E: normal baseline VG-RVPO (<2) plus normal NTproBNP	4 (80.0)	11	15 (−28.6)	1 (20.0)	44	45
F: normal follow-up VG-RVPO (<−3) plus normal NTproBNP	3 (60.0)	12	15 (−28.6)	2 (40.0)	43	45
G: Δ VG-RVPO (<5) plus normal NTproBNP	4 (80.0)	17	21 (±0.0)	1 (20.0)	38	39
H: normal baseline VG-RVPO (<2), follow-up VG-RVPO (<−3) and Δ VG-RVPO (<5) plus normal NTproBNP	5 (100)	18	23 (+9.5%)	0 (0.0)	37	37
I: normal baseline VG-RVPO (<5), follow-up VG-RVPO (<0) and Δ VG-RVPO (<13) plus normal NTproBNP	5 (100.0)	14	19 (−9.5%)	0 (0.0)	41	41

This table presents multiple hypothetical strategies in which the original rule-out criteria of the InShape II study have been changed into new criteria. If the rule-out criteria are met CTEPH is considered ruled out and no further diagnostics should be needed. If the rule-out criteria are not met there is an echocardiography indication for further evaluation of CTEPH according to the InShape II algorithm. Online supplementary data Fig. S4 provides flow-charts of the suggested algorithms. All NTproBNP measurement have been performed during the 3–6 month follow-up moment [α] depicts number of echocardiograms avoided per changed algorithm compared to application of the InShape II algorithm. [β] depicts the number of false negatives per algorithm. ^The cut-off value for a specific VG-RVPO measurement is depicted between the brackets in mV · ms. A value < this number is being considered normal and ≥ this value as abnormal. *Adding an abnormal follow-up VG-RVPO of ≥ −13 mV · ms as a criterium for the echocardiogram on top of the rule-out criteria of InShape II.
CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiogram; VG-RVPO ventricular gradient optimized for right ventricular pressure overload.

patients with suspected PH [19]. Furthermore, VG-RVPO has been shown to be a sensitive measurement for early detection of pulmonary hypertension in systemic sclerosis patients [20,24].

We have three main explanations for our findings. First, the InShape II algorithm had a sensitivity of 100% for CTEPH in the study population, and a specificity of 71%. Therefore, by definition, the sensitivity could not be improved by any test. Of note, this very high sensitivity and moderately high specificity may have been overestimated in the small patient cohort available for analysis.

Second, in contrast to pulmonary arterial hypertension and pulmonary hypertension associated with systemic sclerosis, where the course of disease shows gradual increase of pulmonary artery pressure and change of the vector, the majority of patients with acute PE have acute right ventricle dysfunction, which will show improvement in the course of time [31–34]. Even though most CTEPH patients likely already have CTEPH at the time of the index PE event, a temporary improvement of right ventricle function and pulmonary artery pressure can be expected after initiation of anticoagulant therapy as most patients have acute on chronic PE at presentation [3,7,35–38]. Due to the occurrence of right ventricle dysfunction and recovery in both CTEPH and non-CTEPH post-acute PE patients, the diagnostic value, and in specific the specificity, may have been diluted. Moreover, in acute PE artery obstruction with neurogenic reflexes and myocardial ischemia may result in ECG changes [22,39]. In CTEPH the right ventricular response to chronic increased pulmonary artery pressure first leads to hypertrophy, but when the ventricle is not able to sustain the long-term pressure, the right ventricle starts to dilate with ultimately right ventricle failure as a result [40]. The VG-RVPO detects right ventricle pressure overload due to right ventricle hypertrophy resulting in changes in the action potential duration heterogeneity [21]. Fibrosis, changes in ventricular function and the extend of dilatation also influence the VG-RVPO. The speed and extend of adaptation of the right ventricle as a response to increased pulmonary artery pressure differs among CTEPH patients. Measuring the VG-RVPO 3–6 months after the acute PE event therefore might have resulted in missing elevated pulmonary artery pressure since right ventricular adaptation and remodeling might still be ongoing in some CTEPH patients. Therefore, the additional value of the VG-RVPO for the detection of CTEPH in PE patients may only become apparent after a longer duration of follow-up than available for the study patients. Third and importantly, our study population may have been too small to identify relevant differences. Our study did nonetheless show a numerical higher mean baseline and follow-up VG-RVPO in CTEPH patients compared to non-CTEPH patients, a difference that may become significant when studied in a larger study population.

Strong points of this study are the prospective design of the InShape II study and the novelty of the approach. Some limitations should be taken into account, mainly the small sample size and low number of CTEPH cases leading to reduced statistical power for the performed analysis. Second, over half of the patients included in the InShape II study had to be excluded due to the unavailability of two ECGs since a baseline ECG was not a requisite for InShape II study participation. However, presence of a baseline ECG has not influenced follow-up management or increased the risk of an abnormal VG-RVPO or eventual CTEPH diagnosis. Therefore, no systematic selection bias has been introduced. Moreover, we studied selected patients with a higher likelihood of CTEPH. Consequently, our findings are not generalizable to all PE survivors. Overall, and because of these limitations, our findings should be regarded as hypothesis generating.

Early detection of CTEPH remains crucial for improving outcomes of CTEPH patients [1–3,5–7]. While a larger study with longer follow-up may show a potential role for VG-RVPO, alternative strategies may also be relevant. Mainly, more focus on computed tomography pulmonary angiogram (CTPA) images at baseline may also help identifying patients with CTEPH early in the course of time. We and others showed that signs of chronicity, e.g. the presence of webs/bands, bronchial artery dilatation and right ventricle hypertrophy identified on CTPA images is a strong predictor of a future CTEPH diagnosis [35,36,38]. Indeed, these radiological signs are not effected by anticoagulation therapy and can be evaluated by CTEPH experts as well as by non-specifically trained board-certified radiologists [41–43].

In conclusion, in this predefined analysis of the InShape II study we could not demonstrate additional diagnostic value of VG-RVPO as standalone test or as integrated part of the InShape II algorithm for CTEPH. Future studies with longer follow-up and a larger sample size are needed to ultimately determine the role of VG-RVPO as diagnostic test for CTEPH in PE survivors.

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Author statement

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Dieuwke Luijten: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Fleur M.M. Meijer:** Conceptualization, Investigation, Writing – review & editing. **Gudula J.A.M. Boon:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Yvonne M. Ende-Verhaar:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Roisin Bavalia:** Investigation, Writing – review & editing. **Lahassan H. El Bouazzaoui:** Investigation, Writing – review & editing. **Marion Delcroix:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Menno V. Huisman:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Albert T.A. Mairuhu:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Saskia Middeldorp:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Piotr Pruszcyk:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Dieuwertje Ruigrok:** Investigation, Writing – review & editing. **Peter Verhamme:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Anton Vonk Noordegraaf:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Joris W.J. Vriend:** Investigation, Writing – review & editing. **Hubert W. Vliegen:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Frederikus A. Klok:** Conceptualization, Methodology, Investigation, Writing – review & editing.

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Appendix A. Supplementary data

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