Diagnostic tools in the follow-up and monitoring of congenital heart disease and pulmonary hypertension

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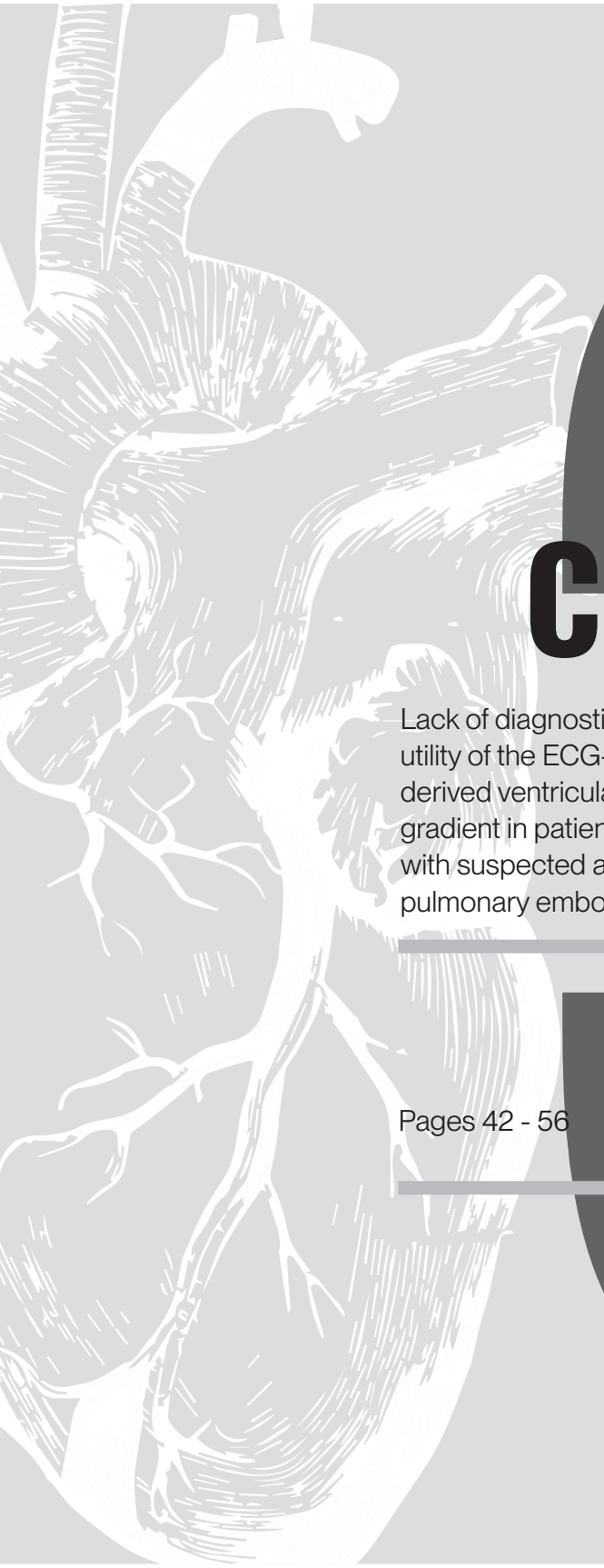

CHAPTER 3

Lack of diagnostic utility of the ECG-derived ventricular gradient in patients with suspected acute pulmonary embolism

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LACK OF DIAGNOSTIC UTILITY OF THE ECG-DERIVED VENTRICULAR GRADIENT IN PATIENTS WITH SUSPECTED ACUTE PULMONARY EMBOLISM

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ABSTRACT

Background

The YEARS algorithm was successfully developed to reduce the number of computed tomography pulmonary angiography (CTPA) investigations in the diagnostic management of patients with suspected pulmonary embolism (PE), although half of patients still needed to be referred for CTPA. We hypothesized that ECG derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO), an easy to use tool for detecting PE-induced pulmonary hypertension (PH), may further improve the efficiency of the YEARS algorithm.

Methods

In this post-hoc analysis of the Years study, ECGs of 479 patients with suspected PE managed according to the YEARS algorithm were available for analysis. The diagnostic performance of VG-RVPO was assessed and likelihood ratios were calculated.

Results

PE was diagnosed in 88 patients (18%). In patients with confirmed PE, 34% had an abnormal VG-RVPO versus 24% of those without PE (odds ratio 1.6; 95%CI 0.94–2.6). The mean VG-RVPO was -22 ± 13 and did not differ between the two patient groups (-22 versus -20; mean difference -2, 95% CI -4.8 to 1.3). The sensitivity of VG-RVPO for PE was 24% (95%CI 34-45), the specificity 76% (95%CI 71-80) and the c-statistic 0.45 (95% CI 0.38-0.51). When combined with the YEARS algorithm, the likelihood ratios of VG-RVPO

remained close to 1.0. Ruling out PE in patients with an indication for CTPA based on a normal VG-RVPO would have resulted in 58 missed cases.

Conclusions
The VG-RVPO has no diagnostic value for suspected acute PE, either as stand-alone diagnostic test or combined with the YEARS algorithm.

Introduction
The objective of diagnostic algorithms for suspected acute pulmonary embolism (PE) is the fast and efficient identification of patients that benefit from early initiation of anticoagulation, avoiding expensive and potentially harmful imaging tests where possible [1, 2]. Conventional algorithms apply a clinical decision rule and D-dimer tests sequentially to identify approximately one third of all patients in whom PE can be ruled out without imaging, using a fixed D-dimer threshold [3-6]. The YEARS algorithm combines assessment of pre-test probability and D-dimer level in parallel, and applies a pre-test probability dependent D-dimer threshold [7, 8]. This algorithm safely excludes PE in half of the patients without performing computed tomography pulmonary angiography (CTPA). However, even with this contemporary diagnostic approach, only one in roughly three CTPA scans was diagnostic of PE, demonstrating an opportunity for improving the specificity of this algorithm [7]. Recent attempts to improve the specificity of the YEARS algorithm by combinations with chest X-ray or other decision rules did not yield a relevant improvement and/or resulted in an unacceptable number of missed diagnoses [9-11]. The combination of YEARS with electrocardiogram (ECG) reading has not been investigated yet.

It has been long recognized that the diagnostic accuracy of 12-lead ECG reading for acute PE is moderate at best [12, 13]. This is mainly due to the fact that there are different etiologies that can underly the pulmonary pressure elevation observed in patients with acute PE. Left ventricular heart disease and advanced interstitial lung disease are other possible clinical features that may affect pulmonary artery pressure [14]. The vector cardiogram (VCG) is a diagnostic tool in which the ECG-derived ventricular gradient is used to detect patients with increased pulmonary pressure, a prevalent condition in patients with acute PE [2]. Previous studies have shown that the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) can detect patients with pulmonary arterial hypertension (PH), with a sensitivity of 62% and specificity of 86% [15-18]. It may be hypothesized that VG-RVPO is a more accurate diagnostic tool for the diagnosis of PE than 'standard' manual ECG reading, and hence, may improve the specificity of the YEARS algorithm.

We therefore set out to measure VG-RVPO in patients with suspected PE managed according to the YEARS algorithm to determine the diagnostic value of VG-RVPO for PE as well as the added diagnostic value of VG-RVPO to the YEARS algorithm.

Methods

Patients and study design

This was a post-hoc analysis of the prospective YEARS study, that included consecutive patients with clinically suspected acute PE between October 2013 and July 2015 [7]. The study design, inclusion and exclusion criteria, outcome measures and baseline population characteristics of the YEARS study have been presented in the original report of the study [7]. Briefly, the attending physician evaluated whether a clinical suspicion of PE was present and if so, the YEARS algorithm was applied (Figure 2). The three criteria from the YEARS algorithm were assessed in all with simultaneous assessment of the D-dimer concentration. According to the algorithm, PE was excluded in patients without YEARS items and D-dimer less than 1000 ng/mL, or in patients with one or more YEARS items and D-dimer less than 500 ng/mL. All other patients were referred for CTPA. Patients in whom PE was ruled out were left untreated and were followed-up for 3 months. Main outcomes of the YEARS study were the number of missed diagnosis and the proportion of patients managed without CTPA.

The current analysis is restricted to patients who were included in our hospital. ECG's were recorded as part of clinical assessment in most of the patients. Patients in whom an ECG could not be retrieved were excluded. Other exclusion criteria were the presence of atrial fibrillation, a pacemaker rhythm, prior myocardial infarction, established severe cardiomyopathy, as these conditions can influence the electrical activity of the ECG. Finally, ECGs that were considered non-interpretable, i.e. with a disrupted electrical signal causing the baselines to shift, were excluded as well. In total 99 (17%) of the originally 578 ECGs that were available were excluded for those reasons. Due to the various aetiologies that can lead to pulmonary pressure elevation, alternative diagnoses were analysed including pulmonary infection (including pneumonia and exacerbation of COPD), decompensated heart failure, acute coronary syndrome, interstitial lung disease, and pulmonary malignancy.

Study objectives

The aim of this study was to investigate the diagnostic accuracy of VG-RVPO for PE in a population of consecutive patients with suspected PE managed according to the YEARS algorithm. Furthermore we aimed to determine the potential incremental diagnostic value of the VG-RVPO to the YEARS algorithm, i.e. whether the posttest probability of PE after an abnormal VG-RVPO would allow for changing the decision to perform CTPA as indicated

by YEARS. Lastly, we evaluated alternative diagnoses than acute PE in patients with abnormal VG-RVPO.
The primary outcome was 1) the mean difference of the VG-RVPO between patients with confirmed PE compared to those in whom the diagnosis PE was rejected and 2) the odds ratio for an abnormal VG-RVPO in patients with PE compared to those without PE and the sensitivity and specificity of VG-RVPO for acute PE.

ECG measurements

Standard 10-second 12-lead ECGs were recorded in the supine position (25mm/second). The first ECG collected within 24 hours after clinical presentation was retrieved from the patient's medical records and analysed. The dedicated software program LEADS (online service: www.leadsecg.com) was used to measure all ECG variables used in this study [19]. The analysis was performed by an independent investigator that was blinded to the patient's identities and clinical course. LEADS not only determines conventional ECG variables (heart rate, heart axis, mean corrected QT interval and QRS duration), which are shown in the results section, but also extracts vector-cardio graphic ECG variables, after mathematically synthesizing a VCG from the ECG. The most relevant VCG variable in the setting of the current study is the ventricular gradient (VG). The VG is defined as the 3D integral of the heart vector over the QT interval. The VG thus gives an indication of the action potential morphology distribution in the heart [16]. With increasing right ventricular pressures this action potential morphology changes, due to mechano-electrical feedback [17, 20]. Previous research has shown that VG can detect right ventricular pressure overload (and, hence, PH) optimally by taking its projection in the 155° azimuth and 27° elevation direction [17, 18, 21]. The projection direction of VG-RVPO points to the right, slightly backward, and slightly downward. In the following, this optimized projection of VG is referred to as VG-RVPO. In normal hearts, VG-RVPO is usually negative, because the VG points more in a leftward direction [22]. With increasing right ventricular pressure, the VG turns more rightward, and VG-RVPO becomes less negative, and, for higher degrees of RV pressure overload, can become even positive. In summary, the more positive the value of the VG-RVPO, the higher and more longstanding the right ventricular pressure overload (Figure 1).

Study definitions

Acute PE was defined as an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by CTPA. Recurrent PE during follow-up was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy [23]. For the purpose of establishing the diagnostic accuracy of VG-RVPO for PE, patients were considered to have acute PE if the diagnosis was confirmed either at baseline or during

Figure. 1. Change in cardiac vectors from the normal physiologic situation to respectively early stage and chronic PH. Abbreviations: PAH, pulmonary arterial hypertension.

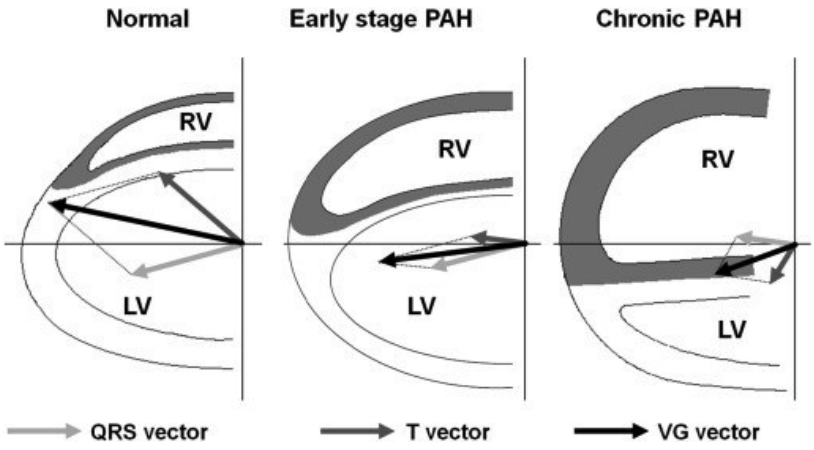
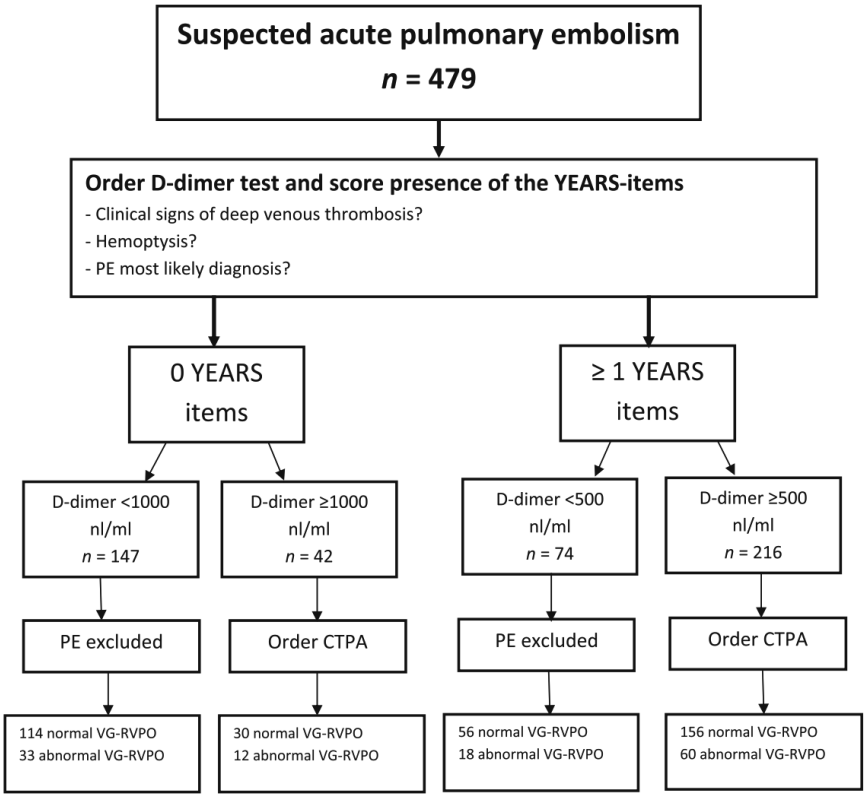


Figure. 2. Study flowchart according to the YEARS Algorithm with additional VG-RVPO analysis.



3-month follow-up. The cut-off value for a normal value of the VG-RVPO was set at -13 mV · ms, with < -13 mV ms being considered normal (PE unlikely) and ≥ -13 mV· ms as abnormal (PE likely). This cut-off value is based on previous research in which the normal value of the ventricular gradient has been published [18, 21, 24-26].

Statistical analysis

Normality of the data was analysed using Kolmogorov-Smirnov test. The results are presented as the mean ± standard deviation (SD) for continuous variables with a normal distribution, as the median (interquartile range) for continuous variables with a non-normal distribution, and as numbers (percentage) for categorical variables. The Mann-Whitney U-test and independent sample t-test were used for comparison of the continuous variables. Measures of OR and of diagnostic performance parameters, e.g. sensitivity and specificity, are reported as point estimates with corresponding 95% confidence intervals (95% CI). Also the area under the curve was estimated with C-statistic. To determine the incremental diagnostic value of VG-RVPO, positive and negative LRs were calculated. From the LRs the posttest probability of an abnormal and a normal VG-RVPO was determined. The pretest probability was dependent on the PE prevalence, which was calculated for the complete cohort as well as for selected patients who were referred for CTPA according to the YEARS algorithm. The LRs indicate by how much the VG-RVPO will change the pretest probability of PE and the indication for CTPA. A LR close to 1 indicates negligible incremental value. Statistical analysis was performed using SPSS version 22.0 (IBM, Chicago, Illinois).

Results

Study Population

Of the 783 YEARS study patients included in our hospital, 578 had an ECG recorded (72%). After exclusion of patients with atrial fibrillation (n=3), pacemaker rhythm (n=4), prior myocardial infarction (n=42), established cardiomyopathy (n=7), complex congenital heart disease (n=5) and non-interpretable ECGs (n=38), 479 patients were included for analysis. Baseline characteristics of the study population are presented in Table 1: their mean age was 51 ±17 years, 287 (60%) were women and 59 (12%) had prior VTE. Details of the diagnostic management of the patients are shown in Figure 2. PE was confirmed by CTPA at baseline in 88 patients (18%), and 2 were diagnosed with VTE during follow-up (0.42%).

ECG Analysis

The results of the ECG analysis are presented in Table 2. During ECG acquisition, the

mean heart rate was 82 ± 17 beats per minute (bpm). The heart rate was higher in patients

Table 1. Baseline characteristics of patients suspected with pulmonary embolism in the Years cohort with ECG availability

	Total Population (n = 479)
Age (years), mean ± SD	51 ± 17
Women, n (%)	287 (60)
Duration of complaints (days), median (IQR)	9
Heart failure with treatment, n (%)	10 (1.8)
Estrogen use, n (%) (% of women)	44 (15.4)
COPD, n (%)	31 (6.5)
Malignancy, n (%)	61 (13.0)
Immobilization or surgery in the past 4 weeks, n (%)	75 (16.0)
Previous VTE, n (%)	59 (12.3)

SD, standard deviation; n, number of patients; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; VTE, venous thromboembolism

Table 2. ECG parameters in the study patients

ECG parameters	All patients (n=479)	No PE (n=391)	PE (n=88)	Mean Difference (95 % CI)
Heart rate (bpm), mean ± SD	82 ± 17	81 ± 17	87 ± 17	-5.2 (-9.3 to -1.2)
QTc duration (ms), mean ± SD	493 ± 81	489 ± 78	515 ± 87	-26 (-46 to -6.2)
QRS duration (ms), mean ± SD	97 ± 17	96 ± 14	100 ± 26	- 3.5 (-7.3 to 0.4)
VG-RVPO (mV · ms), mean ± SD	-22 ± 13	-22 ± 13	-20 ± 14	- 2.0 (-4.8 to 1.3)

ECG, electrocardiogram; PE, pulmonary embolism; bpm, beats per minute; SD, standard deviation; ms, milliseconds; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload

with confirmed PE (87 ± 17 bpm) compared to patients with PE ruled out (81 ± 17 bpm), for an absolute mean difference of 5 bpm (95%CI -9.3 to -1.2). Mean corrected QT interval (QTc) was 493 ms, and also differed between patients with and without PE (absolute mean difference -26, 95%CI -45.9 to -6.2). QRS duration was not significantly different between the patients with and without PE diagnosis.

Primary outcome

The mean VG-RVPO was -22 ± 13 and did not differ between the two patient groups (-22 versus -20; mean difference -2, 95%CI -4.8 to 1.3. For those with confirmed PE (n=88), 34% had an abnormal VG-RVPO versus 24% of those without PE (OR 1.6; 95%CI 0.94–2.6). The sensitivity of VG-RVPO for acute PE was 36% (95% CI 30-43), the specificity was 74% (95% CI 72-76) and the C-statistic was 0.45 (95% CI 0.38-0.51), all indicating insufficient diagnostic accuracy.

Secondary endpoint

Overall, the VG-RVPO was normal in 186 patients (72%) and abnormal in 72 patients (28%) with an indication for CTPA. In the patients were a CTPA was not indicated, 170 patients

Table 3. Distribution of patients in different groups according to the VG-RVPO

ECG results	All Patients (n = 479)	No PE (n = 391)	PE (n = 88)	CTPA indicated (n = 258)	CTPA not indicated (n = 221)
VG-RVPO normal, n (%)	356 (74)	297 (76)	58 (66)	186 (72)	170 (77)
VG-RVPO abnormal, n (%)	123 (26)	94 (24)	30 (34)	72 (28)	51 (23)

ECG, electrocardiogram; n, number of patients; PE, pulmonary embolism; CTPA, computed tomography pulmonary angiography; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload

(77%) had a normal VG-RVPO and 51 patients (23%) an abnormal VG-RVPO (Table 3). Table 4 presents the LR with confidence intervals for the VG-RVPO: all approximated the 1.0, indicating little to no incremental value of VG-RVPO to the YEARS algorithm. If PE would have been considered ruled out in patients with a normal VG-RVPO despite an indication for CTPA according to the YEARS algorithm, 186 CTPA scans would have been additionally saved (38%) at cost of 58 missed cases of PE (65% of all PE cases, failure

Table 4. likelihood ratios and VG-RVPO results in combination with the YEARS algorithm

	All Patients (n= 479)		**Patients in whom CTPA was indicated according to the YEARS algorithm (n=294)**	
Results ECG	Positive LR (95% CI)	Negative L (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
VG-RVPO normal	1.42 (1.01-1.99)	0.87 (0.74-1.02)	1.21 (0.89-1.65)	0.94 (0.84-1.04)

ECG, electrocardiogram; n, number of patients; CTPA, computed tomography pulmonary angiography; LR, likelihood ratio; CI confidence intervals; VG-RVPO, ventricular gradient optimized for right ventricular pressure overload.

Table 5. Alternative diagnosis in patients with abnormal VG-RVPO and pulmonary embolism ruled out

Alternative explanation (n = 94)	**Number of patients n (%)**
Pulmonary infection	6 (6.4)
Acute coronary syndrome	19 (20.1)
Decompensated heart failure	13 (13.8)
Interstitial lung disease	10 (10.6)
Pulmonary malignancy	11 (12)
History of PE	3 (3.2)
Pulmonary Hypertension on echocardiography	2 (2.1)
Obstructive sleep apnea	4 (4.3)
Other: - History of aortic valve replacement - ICD in situ - patent foramen ovale - no alternative explanation	26 (27.6) 1 (1.1) 1 (1.1) 1 (1.1) 23 (24.4)

N, number of patients; SLE, systemic lupus erythematosus; PE, pulmonary embolism

rate 19%, 95%CI 0.15-0.24). If PE would have been considered present in patients with an indication for CTPA according to years and with an abnormal VG-RVPO, 72 CTPA scans would have been avoided but 51 cases (11%) would have been false positive.

The alternative diagnoses in patients with abnormal VG-RVPO but without PE are shown in Table 5: the most frequent alternative explanation was acute coronary syndrome (20%). Previous research stated that the vector and thus VG can change due to ischemia [27, 28]. Other common diagnoses were interstitial lung disease (11%), decompensated heart failure (14%) and lung cancer (12%).

Discussion

In this post hoc analysis of the YEARS study, the diagnostic value of VG-RVPO for PE as stand-alone diagnostic test as well as combined with the YEARS algorithm was very limited. If the VG-RVPO would have been used to rule out acute PE, the failure rate of the algorithm would have been unacceptably high.

Several different ECG abnormalities have been associated with PE. The most frequently mentioned abnormalities are: sinus tachycardia, right bundle branch block, T-wave inversion in leads V1 through V4, S wave in lead I, Q wave in lead III, inverted T in lead III, and S1Q3T3 complex [29, 30]. Notably, many of the described changes are transient and highly prevalent in patients with suspected acute PE. These ECG findings therefore lack sufficient sensitivity and specificity to be of useful diagnostic value [31]. Because of this, ECG findings play no role in the current recommended diagnostic work-up of suspected PE [29, 32]. Their value mainly lies in excluding other causes of dyspnea or chest pain in the initial patient assessment. The QT time was significantly different between the two groups in our study. In both groups the QT interval was also longer compared to the general population. The QT interval is reported to be prolonged in the acute phase of PE, especially in high risk patients due to increased pulmonary pressure, sympathetic nervous system overactivity and myocardial ischemia related to hemodynamic alterations associated with PE [33, 34]. The QT time in general is an important prognostic factor in patients with- and without cardiac diseases [33, 34]. In the patients without PE other factors may be present that prolong the QT interval. Furthermore the end of the T wave is detected at the intersection of the steepest tangent to the descending leg of the T wave with the baseline. Strictly direct comparison of measured QT time with other QT times is therefore not possible [19].

This is the first study investigating the diagnostic value of VG-RVPO in patients with suspected PE. The VG-RVPO specifically measures right ventricular pressure overload,

can be easily made, is inexpensive and immediately available [17]. Moreover, the diagnostic value of ECG-derived VG-RVPO have already been proven in patients with suspected PH. Former studies showed accurate estimation of the mean PAP in patients screened for PH and evaluated with right heart catheterization with the use of ECG-derived VG-RVPO, which also can be used to distinguish between normal RV pressure load, mildly to moderately increased RV pressure load, and severely increased chronic RV pressure load [15,17,18].

Our hypothesis that VG-RVPO would yield a higher specificity than sensitivity was confirmed, However, we found no incremental diagnostic value of the VG-RVPO as stand-alone diagnostic test or combined with the YEARS algorithm for acute PE. The main explanation for this finding is the poor sensitivity of the VG-RVPO, for the detection of PE, which is to be expected, because not all PEs lead to RV pressure overload. For instance, in low risk patients with PE, defined by a sPESI score of 0, acute ventricular overload (RV/LV diameter ratios > 1.0) has been described to only be present in 38% of all patients [35]. The PA pressure increases only if more than 30–50% of the total cross-sectional area of the pulmonary arterial bed is occluded by thromboembolic disease, which explains the normal aspect of the RV in the majority of patients with PE [36,37]. Hence, even despite its accuracy to detect PH, VG-RVPO likely only detects patients with sufficient thromboembolic burden to raise PA pressure. Furthermore 28% of the patients in this cohort with PE excluded had an alternative diagnosis associated with higher PA pressures and therefore abnormal VG-RVPO, e.g. left heart disease, chronic lung disease and hypoxia, resulting in lower specificity. Thus, the incremental diagnostic value of the VG-RVPO for diagnosing PE is limited. Even so, the role of VG-RVPO recorded on admission could potentially be valuable in the risk stratification of PE during hospitalization, although this remains to be studied.

Strong points of our study are the novelty of our data, the prospective design of the YEARS study and the completeness of its follow-up. Furthermore, all endpoints were adjudicated by independent experts. The main limitations are its post-hoc design causing non-availability of ECGs in 205 (28%) study patients, with an additional 38 (4.9%) patients with non-interpretable ECGs. This may have resulted in selection bias. Unfortunately, echocardiography in patients suspected of PE is not routine practice in our hospital. Because of this, no data on pulmonary artery pressure is available. The relatively long duration since symptoms started (9 days), may also have affected our outcomes.
In conclusion, this post-hoc analysis of the YEARS study failed to demonstrate incremental diagnostic value of VG-RVPO for acute PE, either as stand-alone diagnostic test or combined with the YEARS algorithm.

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