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

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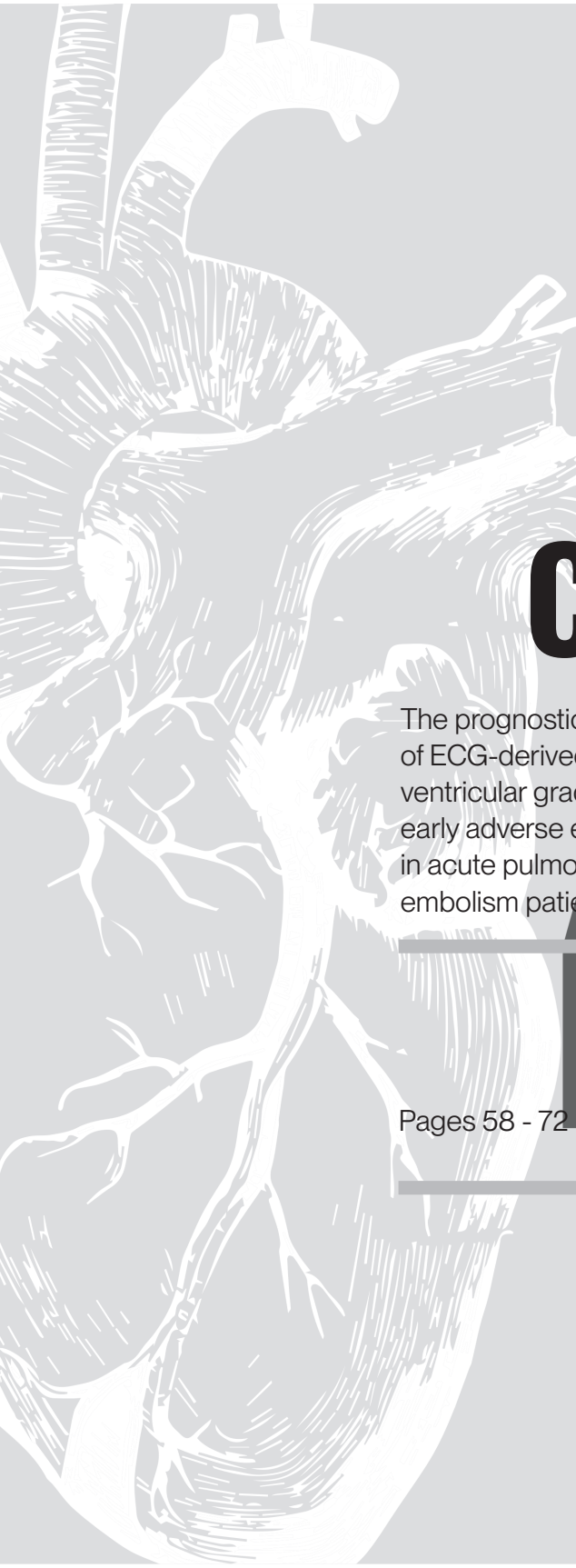

CHAPTER 4

The prognostic value of ECG-derived ventricular gradient in early adverse events in acute pulmonary embolism patients

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THE PROGNOSTIC VALUE OF ECG-DERIVED VENTRICULAR GRADIENT IN EARLY ADVERSE EVENTS IN ACUTE PULMONARY EMBOLISM PATIENTS

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ABSTRACT

Background

Risk-stratification in pulmonary embolism (PE) includes clinical decision rules, biomarkers and signs of right ventricular (RV) overload. The vector electrocardiogram is a diagnostic tool in which the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) can be used to detect patients with increased pulmonary pressure. The primary aim of this study was to assess the association of VG-RVPO and CT-assessed RV/LV diameter ratio as well as the prognostic value of an abnormal VG-RVPO for early adverse events in PE patients.

Methods

In this single-center retrospective study, adult patients with acute PE were identified via the hospital's administrative system. Adverse events were defined as the combined outcome of 30-day overall mortality, recurrent venous thromboembolism, the need for mechanical ventilation, the need for inotropic or vasopressive therapy and/or cardiac resuscitation.

Results

VG-RVPO analysis was available for 164 patients diagnosed with PE between December 2015 and September 2018. Abnormal VG-RVPO was associated with a CTPA-assessed RV/LV diameter ratio >1.0 (OR 2.0; 95%CI 1.0-3.9). The adverse 30-day composite outcome occurred in 16 of 66 patients (24%) with abnormal VG-RVPO compared to 22 of 98 patients (22%) with normal VG-RVPO (OR 1.1, 95%CI 0.53-2.3). The net reclassification

improvement of VG-RVPO on top of RV dilatation for predicting early adverse events was -12%, indicating no additional prognostic value of VG-RVPO on top of RV/LV diameter ratio.

Conclusions
Although we observed an association between RV dilatation, abnormal ECG-derived VG-RVPO was not associated with acute PE associated adverse events.

Introduction
Current treatment guidelines for acute pulmonary embolism (PE) emphasize the importance of proper and simple risk stratification to assess PE severity and guide towards therapeutic decision-making, an improvement of care that has been linked to lower PE-related mortality [1-4]. Current frequently used methods for risk-stratification include clinical decision rules, cardiac biomarkers and radiological findings of right ventricular (RV) overload assessed by echocardiography or computed tomography pulmonary angiography (CTPA).

Electrocardiographic (ECG) parameters may be useful for risk stratification too. The association of specific electrocardiographic changes indicative of RV strain and poor outcome has already been shown in current literature [5]. ECG abnormalities such as T wave inversion in leads V1-V4, a QR pattern in V1, an S1Q3T3 pattern, and incomplete or complete right bundle branch block are associated with increased risk of circulatory shock and mortality in patients with confirmed PE [6].

The vector electrocardiogram (VCG) is an easy to use, cheap and immediately available diagnostic tool in which the ECG-derived ventricular gradient optimized for right ventricular pressure overload (VG-RVPO) is used to detect patients with increased pulmonary hypertension (PH), a prevalent condition in patients with acute PE [1,7]. The diagnostic value of ECG-derived VG-RVPO has been proven in a heterogeneous group with suspected PH but is limited in the setting of suspected acute PE [7-10]. PH causes pressure overload of the RV with an increase in heart rate and the magnitude and direction of the ventricular de-and repolarization forces change. This is due to increased wall stress and hypertrophy [7-9]. It may, therefore be hypothesized that VG-RVPO is an accurate diagnostic tool for estimating the presence and severity of acute right ventricular pressure overload, and can be used for risk stratification of patients with PE.

We set out to measure VG-RVPO in patients with acute PE to determine the prognostic

value of an abnormal VG-RVPO for occurrence of early adverse events.

Methods

Design

In this retrospective cohort follow-up study, patients diagnosed with acute PE between December 2015 and December 2018 in a Dutch academic medical center (Leiden University Medical Center, Leiden, the Netherlands), were identified via the hospital's administrative system. Patients were eligible for inclusion if they were 18 years or older and had established acute symptomatic or incidental PE involving subsegmental or more proximal pulmonary arteries confirmed by computed tomography pulmonary angiography (CTPA) [11]. ECGs were recorded at first day of admission as part of routine clinical assessment in most of the patients. Patients in whom an ECG could not be retrieved were excluded from the current analysis. Furthermore, as some conditions can influence the electrical activity of the ECG and may give a false-positive or negative outcome, the presence of these conditions led to exclusion: atrial fibrillation, a pacemaker rhythm, prior myocardial infarction, established severe cardiomyopathy and complex congenital heart disease. Finally, non-interpretable ECGs were excluded as well. The need for informed consent was waived by the institutional medical-ethical board review of the Leiden University Medical Center due to the retrospective study design.

Study objectives

The primary aim of this study was to assess the prognostic value of an abnormal VG-RVPO, defined as abnormal with a cut-off value off ≥ -13 mV· ms as derived from previous studies, for early adverse events and clinical deterioration in all patients with acute PE, and specifically for normotensive PE patients.7-9 The secondary aims of this study were 1) to assess the optimal cut-off value of VG-RVPO for predicting early adverse events, 2) to assess the correlation between VG-RVPO values and RV/LV diameter ratio measurements on CTPA and to 3) investigate the added prognostic value of an abnormal VG-RVPO on top of right ventricular dilatation on CTPA for the occurrence of early adverse events in all normotensive PE patients.

ECG measurements

The first ECG's within 24 hours after the clinical presentation were obtained from the patient's medical records and analyzed. To measure all ECG variables in this study, we used the dedicated software program LEADS (online service: www.leadsecg.com) [12]. An independent investigator performed all analyses, blinded to the patient's characteristics and outcome. Vector-cardio graphic ECG variables were extracted by LEADS, after

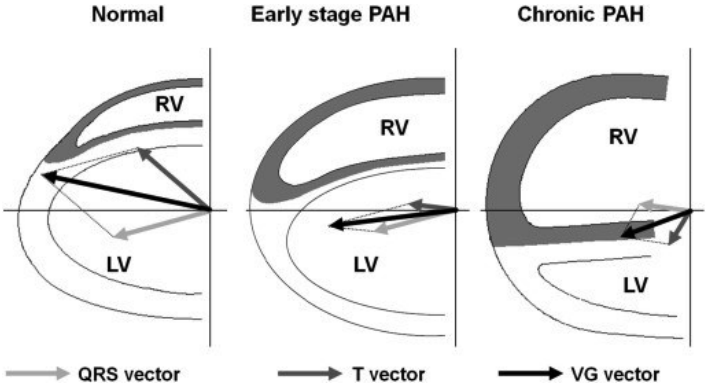
mathematically and automatically synthesizing a vector-cardiogram (VCG) from the ECG. For this study, the ventricular gradient (VG) is the most relevant variable. The VG is defined as the 3D integral of the heart vector over the QT interval. The VG thus indicates the de- and repolarization, i.e. the action potential morphology distribution in the heart [13]. The projection in the 155° azimuth and 27° elevation direction is the most optimal for detecting right ventricular pressure overload because this is the projection directed over the RV. This projection is derived from previous research [7-9]. This optimized projection of VG is referred to as VG-RVPO (ventricular gradient – optimized for right ventricular pressure overload). Normally, the VG-RVPO is negative, with the VG pointing in a leftward direction.14 Increasing right ventricular pressure, the VG turns toward the right, with the VG-RVPO becoming less negative or 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

The definition of acute PE was an intraluminal filling defect of the subsegmental or more proximal pulmonary arteries confirmed by CTPA [15]. Recurrent VTE was defined as a new intraluminal filling defect on CTPA or confirmation of a new PE at autopsy [16]. 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 and ≥ -13 mV· ms as abnormal. This cut-off value is based on previous research in which the normal value of the ventricular gradient has been published [8,9,17-19].

Early adverse events were defined as the combined outcome of 30-day overall mortality, recurrent VTE, the need for mechanical ventilation on the intensive care unit (ICU), the need for inotropic or vasopressive treatment and/or cardiac resuscitation. Right ventricular dilatation was defined as an RV/LV diameter ratio greater than 1.0 with ventricular diameters

Figure 1. Change in cardiac vectors from the normal physiologic situation to respectively early stage and chronic PH. Reprinted from with permission 8



PAH, pulmonary arterial hypertension; RV, right ventricle; LV, left ventricle; VG, ventricular gradient

measured in the transverse plane at the widest points between the inner surface of the free wall and the surface of the interventricular septum [20,21].

Statistical analysis

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.

Crude odds ratios (OR) were provided to describe differences with regard to the primary outcomes with corresponding 95% confidence intervals (95%CI). For the secondary outcomes, the area under the curve was estimated with C-statistic and used as a quantitative measure of test performance for the different cut-off values. We calculated net reclassification improvement (NRI) to determine whether the addition of VG-RVPO values to RV/LV ratio measurements improved discrimination. SPSS version 25.0.0 (SPSS, IBM) was used to perform all analyses.

Results

Study patients

Between December 2015 and September 2018, 180 patients were diagnosed with acute PE by CTPA in our hospital, of whom 16 were excluded due to non-interpretable ECGs or comorbidity influencing the electrical signal of the ECG. Table 1 summarizes the baseline characteristics of the study patients. Their mean age was 64 years (SD 15), 45% was female and 26% had active malignancy at the time of diagnosis. Renal insufficiency (creatinine clearance < 50 ml/min) was present in 14 patients (10%). Ischemic heart disease was present in 22 patients (13%), and heart failure and COPD in 14 (8.5%) and 19 (12%) patients, respectively. Patients with abnormal VG-RVPO were older than those with a normal VG-RVPO with a mean difference of 6.7 years (95CI% -11 to -2.1). Furthermore, heart failure (OR 6.6; 95% 1.8-25) was more prevalent in those with abnormal VG-RVPO. All patients were treated with anticoagulation therapy.

Table 1. Baseline characteristics of patients with PE selected by VG-RVPO

Demographics	Abnormal VG-RVPO N=66	Normal VG-RVPO N=98	Total population N=164
Age, mean (SD)	67.9 (11.7)	61.2 (15.8)	63.8 (14.7)
Female sex, no (%)	32 (48.5)	42 (42.9)	74 (45.1)
Weight in kg, mean (SD)	85.9 (19.2)	81.6 (16.4)	83.3 (17.6)
Body Mass Index, mean (SD)	30.3 (6.1)	26.2 (4.3)	27.9 (5.5)
Creatinine clearance — no. (%)			
<30 ml/min	1 (1.5)	4 (4.2)	5 (3.0)
30-50 ml/min	5 (7.6)	6 (6.1)	11 (6.7)
50-80 ml/min	33 (50.0)	27 (27.6)	60 (36.6)
>80 ml/min	24 (36.4)	59 (60.2)	83 (50.6)
Missing	3 (4.5)	2 (2.0)	5 (3.0)
VTE risk factors			
Previous venous thromboembolism — no. (%)	17 (25.8)	19 (19.4)	36 (22.0)
COPD — no. (%)	11 (16.7)	8 (8.2)	19 (11.6)
Heart failure — no. (%)	11 (16.7)	3 (3.1%)	14 (8.5)
Ischemic heart disease — no. (%)	11 (16.7)	11 (11.2)	22 (13.4)
Estrogen use — no. (%)			8 (4.9)
Immobilisation — no. (%)	12 (18.2)	32 (32.7)	44 (26.8)
Recent surgery — no. (%)	8 (12.1)	21 (21.4)	29 (17.7)
Active malignancy no. — no. (%)	14 (21.2)	29 (29.6)	43 (26.2)
Recurrent or metastatic cancer — no. (%)			23 (14.0)
VTE presentation			
Signs of RV dilatation, RV / LV ratio > 1.0	39 (59.1)	47 (48.0)	86 (52.4)
Extent of qualifying PE no. (%)			
Subsegmental	4 (6.1)	19 (19.4)	23 (14)
Segmental	25 (37.9)	30 (30.6)	55 (33.5)
Central	31 (47)	45 (46.9)	77 (47.0)

Could not be assessed	3 (4.5)	1 (1.0)	4 (2.4)
Days of admission	11 (14.3)	12.6 (11.1)	11.9 (12.5)
Treatment			
LMWH	20 (30.3)	25 (26.5)	45 (27.4)
LMWH/VKA	20 (30.3)	25 (25.5)	45 (27.4)
DOAC	18 (27.3)	40 (40.8)	58 (35.4)
LMWH/DOAC	8 (12.1)	7 (7.1)	15 (9.1)
Thrombolysis	3 (4.5)	2 (2.0)	5 (3)

PE, pulmonary embolism; VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; SD, standard deviation; VTE, venous thromboembolism; COPD, Chronic obstructive pulmonary disease; RV, right ventricle; LV, left ventricle; VKA, vitamin K antagonists; DOAC, direct anticoagulants.

Primary outcome

A total of 18 patients died during the 30-day follow up (11%). One patient was diagnosed with recurrent VTE and ICU admissions were needed in 25 (15%) patients. Of the latter, ten patients were admitted because of the need for inotropic treatment, 14 required mechanical ventilation and seven needed ICU care after cardiac resuscitation. For the

Table 2. Outcomes of study patients stratified according to VG-RVPO

	Abnormal VG-RVPO N=66	Normal VG-RVPO N=98	OR	95% CI
Total 30-day adverse outcome	16	22	1.1	(0.53 – 2.3)
- overall mortality	8	10	1.3	(0.49 – 3.5)
- ICU admission	11	14	1.3	(0.53 – 3.0)
-recurrent VTE	0	1	-	-
-PE-related Mortality	4	5	1.3	(0.34 – 5.1)

VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; CI, confidence interval; ICU, intensive care unit; VTE, venous thromboembolism; PE, pulmonary embolism;

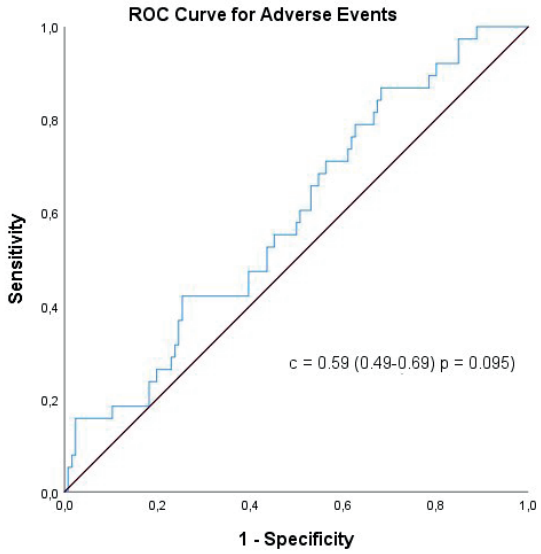
complete cohort, the incidence of the primary outcome was 24% (16 of 66 patients) in those with an abnormal VG-RVPO compared to 22% (22 of 98 patients) with a normal VG-RVPO, for an OR of 1.1 (95%CI 0.53 - 2.3; Table 2). For normotensive PE patients, the incidence of the primary outcome was 15% (7 of 48 patients) for those with an abnormal VG-RVPO compared to 15% (13 of 85 patients) with a normal VG-RVPO, for an OR of 0.95 (95%CI 0.35-2.6).

Secondary outcomes

The overall predictive accuracy of VG-RVPO for early adverse events was moderate with an AUC of 0.59 (0.49-0.69) (Figure 2). The AUC of the predefined threshold of -13 mV · ms showed 42% sensitivity and 60% specificity, resulting in an AUC of 0.51. We were unable to identify a threshold with a relevantly higher AUC.

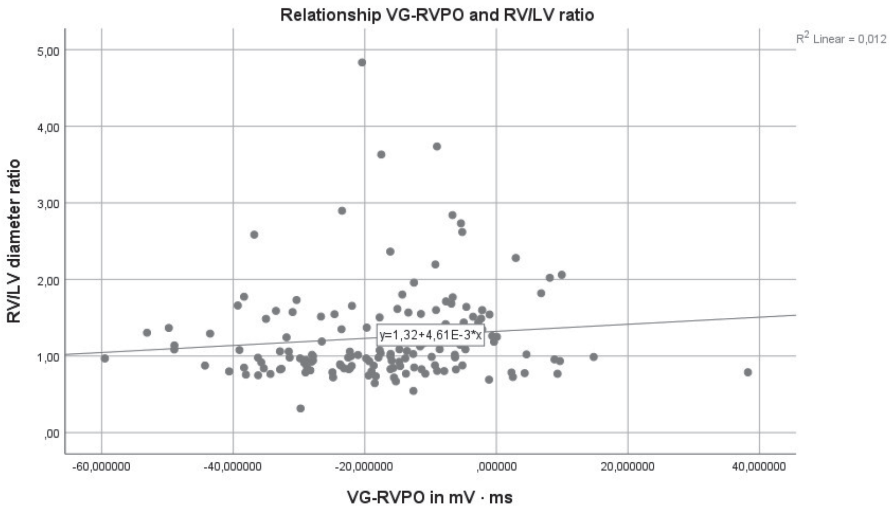
As expected, we found a correlation between VG-RVPO and CTPA-assessed RV/LV diameter ratio. More positive VG-RVPO was associated with higher RV/LV diameter ratio (Pearson correlation value of 0.11, Figure 3) and an RV/LV diameter ratio >1.0 was 2-times more prevalent among patients with an abnormal VG-RVPO than with a VG-RVPO below the predefined threshold (OR 2.0, 95%CI 1.0-3.9).

Figure 2. ROC curve of the VG-RVPO based on occurrence of the 30-day composite end-point for adverse events



VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; ROC; receiver operator curve

Figure 3. Correlation between VG-RVPO and RV/LV diameter ratio



VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; RV, right ventricular; LV, left ventricular

Table 3. Net reclassification improvement shown in detail for adding VG-RVPO to the RV dilatation on CTPA

Event		RV/LV ratio		Total, split	Total
Non-event		Abnormal	Normal		
VG-RVPO	Abnormal	9	6	15	59
		30	14	44	
	Normal	16	6	22	95
		31	42	73	
Total, split		25	12	37	
		61	56	117	
Total		86	68		154

NRI events = (6-16)/86 = -0.116. NRI non-events = (31-14)/68 = 0.25. Overall NRI = 0.134. NRI, net reclassification improvement; VG-RVPO, ECG derived ventricular gradient optimized for right ventricular pressure overload; RV, right ventricular

The NRI of VG-RVPO on top of RV dilatation on CTPA for predicting early adverse events was -12% (Table 3), indicative of the absence of additional prognostic value of VG-RVPO on top of CTPA assessed signs of RV dilatation. The addition of VG-RVPO would have resulted in 6 patients correctly reclassified at high risk for adverse events, in whom an adverse event occurred. In contrast, 16 patients would have been incorrectly reclassified as low-risk who experienced an adverse event within the 30-day follow-up.

Discussion

Although we confirmed the association between VG-RVPO and RV overload as assessed on CTPA, VG-RVPO was not associated with poor adverse outcomes in patients with acute PE. This was observed in the overall population as well as in normotensive patients, the latter for whom risk stratification is most relevant. VG-RVPO had no additional prognostic value on top of RV/LV diameter ratio measurements, which are easily available and currently one of the pillars of PE risk stratification as recommended by international guidelines [22].

Based on current literature we expected a better incremental prognostic value of the VG-RVPO for two main reasons. Firstly, prior studies in which ECG-signs for ventricular strain (S1Q3T3, right bundle branch block (RBBB), or T wave inversions in V1-V4) were analyzed, a significant correlation was shown between the number of ECGs signs of ventricular strain and pulmonary artery pressure in PE patients [23,24]. The association between in-hospital death or clinical deterioration and the presence of these ECG abnormalities have previously been described. A meta-analysis reported ECG signs, i.e. SQQ3T3, complete RBBB, T-wave inversion ,and right axis deviation, as good predictors for in-hospital mortality. Similar findings were observed for clinical deterioration [25]. Besides, Vanni et al reported at multivariate survival analysis an association between right ventricular strain and clinical deterioration and in-hospital mortality (HR 2.58; 95% CI, 1.05-6.36) [5].

Secondly, the association of RV overload and an increased risk of PE-associated early mortality is widely acknowlegded [26]. Previous research has already shown that there is a correlation between VG-RVPO and pressure overload in patients with pulmonary hypertension .7-9,27 The hypothesis in these studies was that the pressure overload of the RV caused by an increase in RV wall tension results in RV hypertrophy and RV dilatation over time. Indeed, the VG-RVPO in patients with PH was significantly higher than in patients without PH [8,9].

Taking a closer look at the association between VG-RVPO and RV dysfunction, the

difference between the acute and chronic setting may be explained by different pathophysiological mechanisms. In the case of acute PH in patients with PE, the ECG changes as a result of obstruction of the pulmonary artery, pulmonary neurogenic reflexes and myocardial ischemia related to hemodynamic alterations associated with PE [28]. In chronic PH there is a structural and functional adaptation of the RV, causing the direction of the vector changes to change (Figure 1) [7,27,29]. This may explain the poor predictive value of VG-RVPO and the outcome of patients with acute PE.

Although we could not observe an incremental prognostic value of an abnormal VG-RVPO for PE patients in the acute setting, VG-RVPO may still be useful for the follow-up of patients with acute PE. The VG-RVPO may, for example, be useful to identify patients with chronic thromboembolic pulmonary hypertension (CTEPH), which occurs in ~3% of patients with PE [30]. CTEPH is still an underdiagnosed disease with a long diagnostic delay. Early diagnosis is of vital importance since diagnostic delay has been associated with a more advanced disease stage at the moment of diagnosis as well as with higher overall mortality [31-33]. The current diagnostic delay of CTEPH is a year or even more, which is reflecting the inefficiency of the current diagnostic tools and the lack of clear guideline recommendations regarding the optimal follow-up of patients with acute PE [34-38]. In this specific patient group, serial measurements of the VG-RVPO may be used to detect early changes in ventricular pressure overload, which may facilitate early detection like previously described in patients with systemic sclerosis [9].

Strong points of this study are the novelty of our data: this is the first study assessing the prognostic value of an abnormal VG-RVPO for early adverse events and clinical deterioration in patients with acute PE. Furthermore, the ECG analysis was done by an independent investigator and all endpoints were adjudicated by independent experts. Some limitations should be taken into account as well. Selection bias is likely present because of the retrospective study design. Also, in some patients ECGs were or of insufficient quality. Lastly, the resulting relative small sample size has led to limited statistical power for the performed analyses.

In conclusion, although we observed an association between RV dilatation and an abnormal ECG-derived VG-RVPO, we could not confirm a higher odds for either an adverse 30-day composite outcome or 30-day overall mortality for those with abnormal VG-RVPO. Also, we could not establish an incremental prognostic value of abnormal VG-RVPO either as a stand-alone test or in addition to CTPA assessed RV dilation for the risk stratification of PE patients.

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