

Predictive Capability of Cardiopulmonary and Exercise Parameters From Day 1 to 6 Months After Acute Pulmonary Embolism

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ABSTRACT: We hypothesized that the slope of relation ventilation to carbon dioxide output (V'_E/V'_{CO_2} -slope) could be predictive already during the very first days after submassive pulmonary embolism (PE) to right ventricular systolic pressure (RV_{sys} by echocardiography) after 6 months. We evaluated 21 hemodynamically stable patients at admittance, at days 3, 7, 90, and 180 by cardiopulmonary exercise testing and echocardiography. V'_E/V'_{CO_2} -slope (48.4 ± 10.8) decreased within the first week (43.0 ± 9.8 at day 7) and normalized until follow-up at 6 months (35.0 ± 11.3 ; $P < 10^{-4}$), $p_{(a-ET)CO_2}$ remained abnormal between days 1 and 3 (5.0 ± 3.9 to 6.7 ± 5.3 mmHg). RV_{sys} declined from 41.7 ± 14.3 to 26.3 ± 13.1 mmHg ($P < 10^{-4}$) at 6 months. V'_E/V'_{CO_2} -slope ($r^2 = 0.27$; $P < .02$) and RV_{sys} ($r^2 = 0.28$; $P = .03$) at day 7 correlated with RV_{sys} at 6 months. $p_{(a-ET)CO_2}$, $p_{(a-ET)O_2}$, V'_D/V'_T were not related to RV_{sys} after 6 months. RV_{sys} 6 months after acute PE is positively correlated with the V'_E/V'_{CO_2} -slope at day 7.

KEYWORDS: Acute pulmonary embolism, V_E/V_{CO_2} -slope, pulmonary hypertension, cardiopulmonary exercise testing, follow-up

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Introduction

Following pulmonary embolism (PE), 1.0–8.8% of patients will develop chronic thromboembolic pulmonary hypertension (CTEPH).^{1–4} The transition from acute to chronic disease is still a point of debate, and CTEPH is frequently underdiagnosed and undertreated.¹ Little is known about the acute cardiopulmonary response and whether this can predict complications in later follow-up.⁵ However, early detection of patients who are at risk of developing CTEPH is important, and it is possible that incomplete recovery between the acute event and hospital discharge may already correlate with long-term deterioration. Therefore, it may be useful to examine the patient not only at a single point during follow-up but during the first days and weeks after PE.

Parameters indicating the risk of CTEPH can be derived from patients' clinical status, echocardiography and plasma markers (brain natriuretic peptide [BNP] and troponin), and from cardiopulmonary exercise testing (CPET).^{6,7} Echocardiography and biochemical markers reflect right ventricular (RV) dysfunction, and altered echocardiographic parameters at hospital discharge have been associated with higher 3-year mortality,⁸ but this correlation is still controversial in patients without systemic hypotension.^{9,10} Early mortality is increased among patients whose RV dysfunction is accompanied by elevated levels of N-terminal BNP^{11,12} or troponin,¹³ but the association with future CTEPH is uncertain. In contrast to echocardiography and plasma markers, the

measurement of blood gases and respiratory gas exchange reflects the pathophysiology of the lung itself. Older studies have evaluated some of these parameters at rest, but none of end tidal pressure of carbon dioxide ($p_{ET}CO_2$),^{14–16} arterio-alveolar oxygen pressure difference ($p_{(a-ET)O_2}$)¹⁷ or the ratio of dead space ventilation to tidal volume (V'_D/V'_T)^{18,19} have been found to be predictive for CTEPH. Studies assessing these parameters during stepwise incremental maximal exercise testing found that physiological dead space (V'_D/V'_T) and $p_{(a-ET)O_2}$ at peak exercise strongly differentiated patients with and without CTEPH after PE,²⁰ and that the capillary to end tidal carbon dioxide gradient ($p_{(c-ET)CO_2}$) was significantly increased in CTEPH compared with idiopathic pulmonary arterial hypertension.²¹ Likewise, the slope of the linear relationship between ventilation (V'_E) and carbon dioxide output (V'_{CO_2}) during incremental exercise, which is regarded as a precise parameter assessing pulmonary perfusion and ventilation-perfusion-mismatch, has been established as a follow-up parameter in chronic PE.^{22,23} In contrast to parameters at maximum exercise level such as peak V'_{O_2} , the V'_E/V'_{CO_2} slope is a submaximal effort-independent measure which indicates breathing drive during exercise. Therefore, we assume that the relation of V'_E/V'_{CO_2} at the anaerobic threshold ($V'_E/V'_{CO_2}@AT$) could be related to the development of CTEPH. So far, neither V'_E/V'_{CO_2} slope nor $V'_E/V'_{CO_2}@AT$ have been studied in the acute phase of PE and the first days following acute PE.



Against this background, we designed this study to include simple, non-invasive and specific parameters linked to both PE and CTEPH. We hypothesized that the V'_E/V'_{CO_2} slope during the first days after submassive PE could already be predictive of RV systolic pressure (RV_{sys} , measured with echocardiography) after 6 months. The secondary hypothesis was to evaluate the relationship between other parameters of breathing, $V'_E/V'_{CO_2}@AT$, V'_D/V'_T , $P_{(c-ET)CO_2}$ and $P_{(c-ET)O_2}$, early after the PE event and RV_{sys} after 6 months.

Methods

Study population

The study was approved by the local ethics committee (Ethikkommission Charité, No. 160/3) and informed written consent was obtained from all patients. Our study included stable patients with acute PE of low- and intermediate risk, for example, with stable systolic blood pressure (SBP) > 100 mmHg (without catecholamine administration), heart rate (HR) < 100/min, capillary oxygen saturation > 90% (without oxygen supplementation) and full consciousness (Pulmonary Embolism Severity Index [PESI] < 85 points).²⁴ Patients had to be effectively treated either with unfractionated heparin intravenously (i.v.) or with low molecular weight heparin (LMWH) subcutaneously. Exclusion criteria were high risk PE (eg, requiring thrombolytic therapy or surgical intervention), severe chronic obstructive pulmonary disease with home-care oxygen supply or forced expiratory volume in 1 second (FEV1) < 1000 mL/s, malignancies that limit prognosis or PESI > 86 points. In addition, patients younger than 18 years and pregnant women were excluded.

Patients were examined at the Charité University Medicine Berlin, Campus Virchow, Department of Cardiology and sequentially studied at five predefined time points: at admittance to the intensive care unit (ICU, day 1), during hospitalization (days 3 and 7) and after 3 and 6 months during outpatient follow-up. Diagnosis of PE was confirmed by computed tomographic angiography in 20 patients and by combined ventilation-perfusion scintigraphy in one patient.

Control population

Parameters of respiration and gas exchange depend on age, gender, body weight and height, and an exact definition of reference values is essential. For V'_E/V'_{CO_2} , V'_D/V'_T , $P_{(a-ET)CO_2}$ and $V'_E/V'_{CO_2}@AT$, these were taken from the Study of Health In Pomerania (SHIP)-study by Koch et al²⁵ (n = 1708, bicycle), for V'_E/V'_{CO_2} slope and $V'_E/V'_{CO_2}@AT$ from Sun et al²⁶ (n = 474, bicycle and treadmill), and for V'_E/V'_{CO_2} slope from Habedank²⁷ (n = 101, treadmill).

Treatment of PE

If heparin was administered continuously i.v., a two- to three-fold prolongation of the activated partial thromboplastin time

(aPTT) had to be achieved; heparin dose was adjusted every 12 hours if it was in the therapeutic range, and 3 hours after correction if it was out of the therapeutic range. If LMWH was administered, an anti-Xa-activity of 0.3 to 0.7 IU/mL had to be achieved; the dose was corrected at 12-hour intervals if necessary. Oral anticoagulation with phenprocoumon or rivaroxaban was started between day 3 and 7. For patients on vitamin K antagonists, patients' general practitioners were responsible for checking the international normalized ratio (INR), which was documented at outpatient visits in our department. Oral anticoagulation was withdrawn after 6-9 months in patients with idiopathic thromboembolism. Supportive medication during the ICU stay included oxygen supply between 2 and 6 L/min if oxygen saturation was < 93%, i.v. volume expansion with full electrolyte solution, and, if necessary, antihypertensive medication. Mobilization of patients started at day 2 or 3 and was completed before discharge from hospital. All patients were advised to wear compression stockings for at least 1 year.

Resting and exercise protocols

At days 1 and 3 after admission, patients sat in a half-supine position and breathed for at least 3 minutes into a bed-side, mobile metabolic cart (MedGraphics Cardio₂, Minnesota, USA), with a simultaneous subcutaneous oxygen saturation measurement (Draeger Oxysat 2, Draeger, Lübeck, Germany). In order to simulate a minimal effort, patients were asked to sit in a completely upright position while measurement was continued for a further 3 minutes. Data from this "minimal exercise" were used to calculate a slope of the linear regression between V'_E and V'_{CO_2} . In addition, at day 7 and after 3 and 6 months, a symptom-limited cardiopulmonary exercise test was performed on a treadmill (MedGraphics, as above) according to the modified Naughton protocol.²⁸ Prior to each test, the equipment was calibrated according to the manufacturer's standards with reference gas and volume calibration. For the measurements at days 1 and 3, the mobile measurement unit was moved to the ICU, and a new calibration was performed at bed-side due to changed environmental conditions. All exercise tests on the treadmill started with a phase of 3 minutes quiet standing and breathing into the mask to reach steady-state conditions. These data were analyzed and are referred to as "resting parameters." Exercise time was recorded and symptoms at peak exercise were documented. All patients were monitored with a continuous 12-lead electrocardiogram (ECG; CardioPerfect, Welch Allyn, New York, USA).

Measurement of gas exchange

Airway flow, V'_{O_2} and V'_{CO_2} , and end tidal expiratory gas concentrations $P_{ET}O_2$ and $P_{ET}CO_2$ were measured breath by breath. Ventilation per minute (V'_E) and the V'_E/V'_{CO_2} ratio were calculated automatically from airway flow and partial gas concentrations. Respiratory gas exchange variables were acquired breath by breath and averaged over 10-second

intervals. For peak \dot{V}'_{O_2} , peak \dot{V}'_{CO_2} and peak \dot{V}'_E , the highest readings of each parameter in the final 30 seconds of exercise were used. The respiratory exchange ratio (RER) was calculated as quotient peak \dot{V}'_{CO_2} / peak \dot{V}'_{O_2} . Ventilatory efficiency during exercise was measured by plotting \dot{V}'_E against \dot{V}'_{CO_2} , excluding values due to acidotic hyperventilation beyond the lactate metabolic threshold, and the slope of the revealed linear relationship ($\dot{V}'_E/\dot{V}'_{CO_2}$ slope) was calculated by linear regression and accepted if the correlation coefficient r was >0.95 . The relation of $\dot{V}'_E/\dot{V}'_{CO_2}$ is lowest at the AT and was reported as $\dot{V}'_E/\dot{V}'_{CO_2}$ @AT. The AT reflects the transition from aerobic to anaerobic metabolism and was determined manually by the V-slope method according to current guidelines. If the V-slope method could not be applied, AT was defined as the lowest point of the ventilatory equivalent for oxygen ($\dot{V}'_E/\dot{V}'_{O_2}$). Two of three independent observers (D.H., T.K., Th.K.) identified the AT in every case.

Blood gas analysis and plasma markers

Arterial blood samples were taken from the radial artery at time of respiratory gas measurement when the resting steady state was reached and were analyzed by Radiometer Copenhagen (ABL 750, Radiometer GmbH, Krefeld) to assess pH value and partial pressures of carbon dioxide (p_aCO_2) and oxygen (p_aO_2). The proportion of dead space V'_D/V'_T was calculated from arterial and end tidal partial pressures of carbon dioxide as $V'_D/V'_T = (p_aCO_2 - p_{ET}CO_2) / p_aCO_2$.²⁴ Samples for the measurement of serum plasma markers such as troponin I, D-dimer and C-reactive protein (CRP) were taken during routine venous blood sampling at hospital admittance, centrifuged at 3000 min⁻¹, cooled to 18°C and analyzed immediately.

Echocardiography

Echocardiography was performed immediately before gas exchange analysis at all five study time points (day 1 [ICU], days 3 and 7, and during follow-up at months 3 and 6) using a Vivid S6 echocardiograph (GE Healthcare Germany, Solingen). Diameters of left and right ventricles were measured in the parasternal short (left ventricular end-diastolic diameter [LVEDd], right ventricular end-diastolic [RVEDd]) and long (LVEDd) axis, and ejection fraction was calculated automatically by the Simpson method²⁹ in the apical four-chamber view. Mitral and tricuspid regurgitation were assessed semi-quantitatively by proximal jet width³⁰ and proximal isovelocity surface area (PISA),³¹ and the severity was classified as mild (I°), moderate/medium (II° and III°) and severe (IV°) according to ACC/ESC recommendations.³² RV_{sys} was estimated by simplified Bernoulli equation via tricuspid regurgitation velocity v as $RV_{sys} [mmHg] = 4v^2$ without addition of central venous pressure. Paradox movements of the interventricular septum were classified as degree I in case of mild systolic shift and degree II in case of systolic compression of the left ventricle.

Tricuspid annular plane systolic excursion (TAPSE) was measured in apical 4-chamber view M-mode with the septum centered.

Statistical analysis

All numeric data are expressed as mean \pm standard deviation for parametric variables, and as median with interquartile range (IQR) in brackets for skewed distributions (non-parametric variables). The normality of the data was verified with the Kolmogorov-Smirnov-test. Changes over time of quantitative parameters (exercise, echocardiographic and laboratory parameters) were identified by repeated measurements analysis of variance (ANOVA) for the entire follow-up and by Student's paired t-test for differences between sequential visits. In the case of non-parametric distribution, changes over time were calculated using the Wilcoxon signed-rank test. A correlation with echocardiographic RV_{sys} at 6 months was tested for the following parameters: circulation (HR, blood pressure [BP]), respiratory rate, laboratory values (Troponin, D-dimer), blood gases (p_aCO_2 , p_aO_2), respiratory gases ($p_{ET}O_2$, $p_{ET}CO_2$), gas exchange and perfusion, V'_D/V'_T , $\dot{V}'_E/\dot{V}'_{CO_2}$ slope, $\dot{V}'_E/\dot{V}'_{CO_2}$ @ AT, $p_{(a-ET)}CO_2$, and echocardiographic parameters of RV dysfunction (RVEDd, RV_{sys} , TAPSE). Spearman's correlations were necessary for the non-Gaussian laboratory parameters Troponin and D-dimer. Univariate linear regression was utilized to evaluate the relationship between RV_{sys} at 6 months and different parameters at baseline, at days 3 and 7 and at 3 months. A P -value $< .05$ was considered significant. All analyses were performed using SPSS 18 (SPSS Inc., Chicago, USA).

Results

Clinical findings at admittance

We examined 21 patients (14 female, mean age 64.2 ± 18.9 years, range 21.6-88.8 years) from ICU to outpatient follow-up. Thromboembolism was found in the Truncus pulmonalis in two patients, in one or both Aa. pulmonales in five patients, in two lobar pulmonary arteries in 11 patients, and in subsegment branches of the pulmonary artery in three patients. Sources of the emboli were (regarding the most proximal localization) V. iliaca in one patient, V. femoralis (communis or superficialis) in 11 patients, V. poplitea in three patients, and peripheral or superficial veins (V. tibialis anterior, saphena magna) in three patients. The embolic origin could not be detected in three patients. Two patients reported taking a long-distance flight immediately before admission. All other thromboembolic events ($n=13$) were classified as idiopathic. All patients were screened for markers of thrombophilia, and a phospholipid antibody syndrome was identified in three patients, while a factor V (Leiden) mutation, a protein S deficiency and a plasminogen activator inhibitor I mutation were found in one patient each. The time between onset of

Table 1. Basic clinical data at time of first examination.

PARAMETER	MEAN \pm SD	MEDIAN (IQR)	RANGE	UNIT
BMI	27.0 \pm 4.4		20.7-39.0	kg/m ²
NYHA-class	3.1 \pm 0.6		2-4	
Heart rate	96.8 \pm 16.2		75-130	1/min
Systolic blood pressure	132.4 \pm 24.5		96-188	mmHg
Respiratory rate	18.2 \pm 4.3		10-26	1/min
p _a CO ₂	29.8 \pm 3.4		23.6-37.0	mmHg
p _a O ₂	68.6 \pm 26.5		41.0-146.0	mmHg
p _{ET} CO ₂	25.3 \pm 6.4		18-36	mmHg
RV _{sys}	41.7 \pm 14.3		20.0-75.0	mmHg
D-dimer		6.25 (6.15)	2.6-16.0	ng/mL
Troponin I		0.075 (0.66)	0.0-1.2	ng/mL
C-reactive protein	3.9 \pm 5.6		0-26	mg/dL
Hemoglobin	13.5 \pm 1.8		10-17.9	mg/dL
LVEF	65.1 \pm 6.0		49-71	%
LVEDd	44.3 \pm 5.2		33-50	mm

BMI: body mass index; LVEDd: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; p_aCO₂: arterial partial pressure of carbon dioxide; p_aO₂: arterial partial pressure of oxygen; p_{ET}CO₂: end-tidal partial pressure of carbon dioxide; RV_{sys}: right ventricular systolic pressure. Mean \pm standard deviation is shown in case of normal distribution, otherwise data are medians with interquartile range (IQR) in brackets.

symptoms and admission to ICU was 10.9 \pm 7.4 hours. Basic clinical data at time of first examination are shown in Table 1. A pathologic ECG, defined as main vector $> 90^\circ$ or sagittal type, right bundle branch block or new onset negative T in leads V1 to V3, was found in 16 of the 21 patients.

Clinical findings at follow-up

All patients survived, had no re-occurrence of thromboembolism and underwent exercise testing at 6 months. At this time, 10 (48%) patients were in New York Heart Association (NYHA) class "0" (*M*: class I, range 0–III), ECG changes (as defined above) persisted in two (9.5%) patients, and resting cardiopulmonary parameters were normalized (SBP 124 \pm 19 mmHg, diastolic BP 77 \pm 7.5 mmHg, HR 87 \pm 16 beats/min, respiratory rate 14 \pm 4 beats/min). Detailed clinical data are shown in Table 2.

Pulmonary gas exchange at rest and during exercise

The minimal in-bed exercise at day 3 lead to a decline of p_{ET}O₂ from 120.1 \pm 10.6 to 119.7 \pm 9.8 mmHg and an increase of p_{ET}CO₂ from 25.5 \pm 5.5 to 26.0 \pm 6.0 mmHg, which was

acceptable as metabolically demanding and therefore allowed a calculation of V'_E/V'_{CO_2} slope.

At admittance (day 1), resting p_(a-ET)CO₂, p_(a-ET)O₂, V'_E/V'_{O_2} and V'_D/V'_T were higher than normal values, while p_{ET}CO₂ and p_{ET}O₂ were lower. Between days 1 and 3, p_(a-ET)CO₂ remained abnormal (increasing from 5.0 \pm 3.9 to 6.7 \pm 5.3 mmHg; *P*=n.s.), whereas p_(a-ET)O₂ declined (from 59.5 \pm 19.8 to 47.9 \pm 16.1 mmHg; *P*=0.001).

p_{ET}CO₂@AT and p_{ET}O₂@AT normalized within 1 week. Remarkably, the initially high V'_E/V'_{CO_2} slope (48.4 \pm 10.8) decreased slowly within the first week (to 43.0 \pm 9.8 at day 7) and normalized by follow-up at 3 (35.8 \pm 11.1) and 6 months (35.0 \pm 11.3; *P*<10⁻⁴, Figure 1). The V'_E/V'_{CO_2} @AT showed a comparable decline from 46.4 \pm 12.7 at day 3 to 35.3 \pm 8.1 at 6 months (*P*<.01, Figure 2).

Spirometric parameters such as FEV1 and FVC did not change significantly from day 7 to 6 months (2.3 \pm 0.6 to 2.4 \pm 0.8 L/s and 2.9 \pm 1.0 to 3.1 \pm 1.1 L, respectively); these are presented in detail in Table 3. At 6 months, the mean exercise duration was 9.1 \pm 6.1 min, with a mean treadmill speed of 2.0 miles/h (3.2 km/h) and an incline of 7%.

The complete time-course of respiratory parameters and normal values is shown in Figures 3 and 4.

Table 2. Clinical data in follow-up.

PARAMETER	DAY 1	DAY 3	DAY 7	3 MONTHS	6 MONTHS	ANOVA P
BMI (kg/m ²)	27.0 ± 4.4	27.5 ± 4.9	26.5 ± 4.4	27.4 ± 4.7	26.9 ± 4.8	n.s.
NYHA-class	3.1 ± 0.6	2.8 ± 0.6	2.3 ± 0.9	1.2 ± 1.0	0.9 ± 1.0	n.s.
Heart rate (1/min)	96 ± 16	84 ± 11	89 ± 13	91 ± 19	87 ± 17	<0.05
Systolic blood pressure (mmHg)	132 ± 24	127 ± 18	120 ± 15	118 ± 13	124 ± 19	<0.01
Diastolic blood pressure (mmHg)	79 ± 17	74 ± 9	74 ± 8	74 ± 7	76 ± 6	n.s.
Respiratory rate (1/min)	18 ± 4	19 ± 4	18 ± 5	14 ± 3	14 ± 4	<0.05
ECG signs of right heart congestion (n)	16/21	6/21	4/21	2/21	1/20	<0.01*

ANOVA: analysis of variance; BMI: body mass index; ECG: electrocardiogram; NYHA: New York Heart Association. ECG signs of right ventricular congestion: see results first paragraph. Date are shown as mean ± standard deviation. *Chi-square-test.

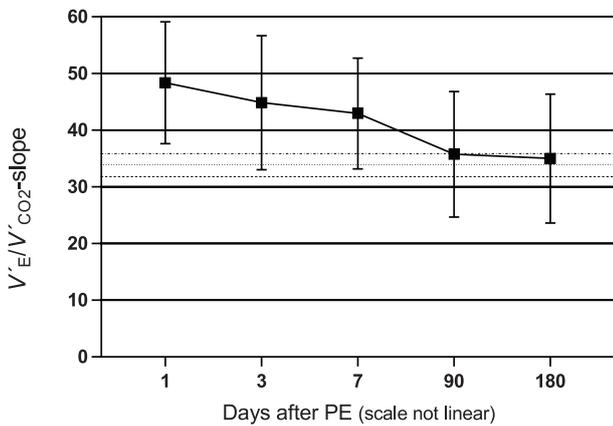


Figure 1. V'_E/V'_{CO_2} —slope over time (bold line, error bars indicating 1 SD).

Normal values:
 • Koch 2009 (upper 95th percentile).
 •• Habedank 1998 (mean + 1SD).
 --Sun 2002 (mean + 1SD).

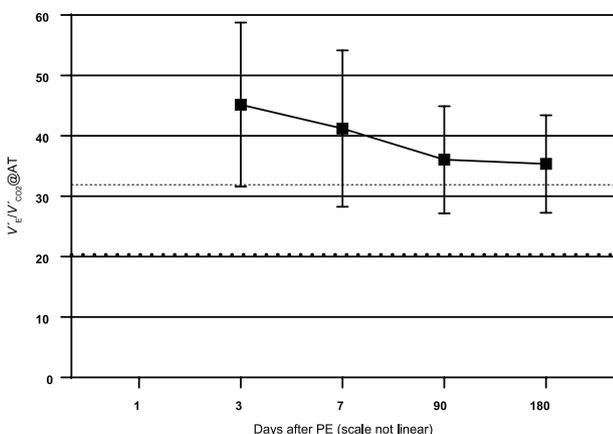


Figure 2. $V'_E/V'_{CO_2}@AT$ over time (bold line, error bars indicating 1 SD).

Normal values:
 – Koch 2009(upper 95th percentile).
 -- Sun 2002(mean + 1SD).

Echocardiography

RV dilatation (diastolic diameter RVEDd > 30 mm) was found in 17 of 21 (81%) patients at baseline (35.9 ± 4.2 mm overall) and normalized in all patients within 6 months (27.9 ± 3.9 mm, $P < 10^{-4}$). In parallel, there was a decline in RV systolic pressure from 41.7 ± 14.3 mmHg at baseline to 32.1 ± 12.8 mmHg at day 7. At 6 months, the mean RV_{sys} had normalized to 26.3 ± 13.1 mmHg ($P < 10^{-4}$), but remained elevated (±30 mmHg) in seven (33%) patients. Changes over time in the parameters describing RV function (RVEDd, RV_{sys} , TAPSE) are shown in Figure 5.

Laboratory markers

Troponin I, a marker of myocardial (ie, RV) damage, was initially elevated in 15 of 21 (71%) patients. Mean troponin I levels decreased from 0.075 (0.66) mg/mL at first examination to 0.0 (0.15) mg/mL at day 3 (Wilcoxon, $P = .001$) and remained below the cut-off at subsequent time points. Similarly, the D-dimer level decreased from 6.3 (6.2) initially to 4.0 (3.3) at day 3 and normalized by day 7. CRP and hemoglobin remained unchanged.

Parameters potentially predicting CTEPH (correlation with RV_{sys} at 6 months)

Primary hypothesis. The V'_E/V'_{CO_2} slope at day 3 correlated weakly but statistically significantly to RV_{sys} at 6 months ($r^2 = 0.19$; $P = .047$); this correlation remained weak but statistically significant for the V'_E/V'_{CO_2} slope measured at day 7 ($r^2 = 0.27$, $P < .02$), at 3 months ($r^2 = 0.28$; $P < .02$) and at 6 months ($r^2 = 0.3$; $P < .01$).

Secondary hypothesis. As measured at admission, the parameters assessed in the secondary hypothesis had close to zero

Table 3. Respiratory, echocardiographic and blood gas data in follow-up.

PARAMETER	DAY 1	DAY 3	DAY 7	3MONTHS	6MONTHS	UNIT	ANOVA P
p_aO_2	66.3 ± 15.2	72.3 ± 14.0	–	–	–	mmHg	0.03
p_aCO_2	29.5 ± 4.2	32.4 ± 5.0	–	–	–	mmHg	<10 ⁻³
$p_{ET}O_2$ @rest	124.2 ± 13.9	120.1 ± 10.6	114.7 ± 8.2	114.8 ± 9.3	114.7 ± 11.0	mmHg	0.01
$p_{ET}O_2$ @AT	–	119.7 ± 9.8	111.5 ± 11.2	110.5 ± 11.0	111.1 ± 11.1	mmHg	0.02
$p_{ET}CO_2$ @rest	24.6 ± 5.7	25.8 ± 5.5	28.1 ± 5.7	29.8 ± 5.6	29.1 ± 5.3	mmHg	0.01
$p_{ET}CO_2$ @AT	–	26.0 ± 5.9	30.0 ± 6.8	33.7 ± 7.3	33.0 ± 7.4	mmHg	<0.01
V'_E/V'_{CO_2} slope	48.4 ± 10.8	44.9 ± 11.8	42.9 ± 9.8	35.8 ± 11.1	35.0 ± 11.4	–	<10 ⁻⁴
V'_E/V'_{CO_2} @AT	–	45.2 ± 13.6	41.2 ± 13.0	36.0 ± 8.8	35.4 ± 8.1	–	<0.01
$p_{(a-ET)}O_2$	59.5 ± 19.8	47.9 ± 16.0	–	–	–	mmHg	<10 ⁻³
$p_{(a-ET)}CO_2$	5.0 ± 3.9	6.7 ± 5.3	–	–	–	mmHg	n.s.
V'_D/V'_T @rest	0.17 ± 0.13	0.20 ± 0.15	–	–	–	–	0.01
RVEDd	36.1 ± 4.6	33.6 ± 4.8	32.7 ± 5.3	29.0 ± 3.1	28.1 ± 3.8	mm	<10 ⁻³
TAPSE	15.1 ± 3.6	17.7 ± 3.4	18.9 ± 2.9	19.7 ± 2.0	20.0 ± 2.3	mm	<10 ⁻³
PAP_{sys}	41.7 ± 14.3	36.7 ± 13.8	32.1 ± 12.8	26.2 ± 11.8	26.3 ± 13.1	mmHg	<10 ⁻³
FEV1	–	2.1 ± 0.6	2.3 ± 0.6	2.4 ± 0.8	2.4 ± 0.8	L/s	n.s.
FVC	–	2.9 ± 0.9	2.9 ± 1.0	3.0 ± 1.0	3.1 ± 1.1	L	n.s.

ANOVA: analysis of variance; FEV1: forced expiratory volume at 1 second; FVC: forced vital capacity; p_aCO_2 : arterial partial pressure of carbon dioxide; $p_{ET}CO_2$: end tidal pressure of carbon dioxide; $p_{(a-ET)}O_2$: difference of arterial and end tidal pressure of oxygen; $p_{(a-ET)}CO_2$: difference of capillary and end tidal pressure of carbon dioxide; p_aO_2 : arterial partial pressure of oxygen; PAP_{sys} : systolic pulmonary arterial pressure; $p_{ET}O_2$: end tidal pressure of oxygen; RVEDd: right ventricular end-diastolic diameter; RV_{sys} : right ventricular systolic pressure; TAPSE: tricuspid annular plane systolic excursion; V'_D : dead space ventilation; V'_T : tidal volume. Data are shown as mean ± standard deviation.

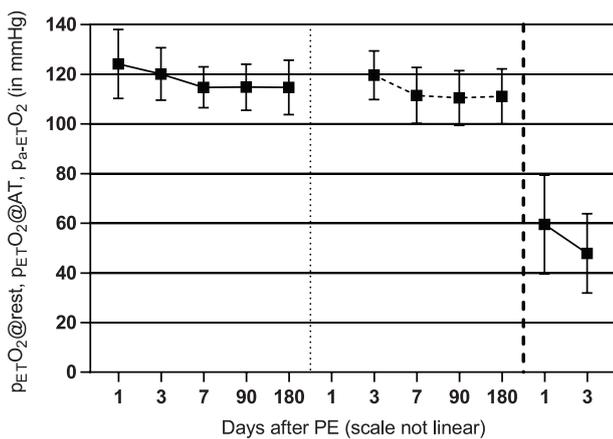


Figure 3. Oxygen exchange. $p_{ET}O_2$ @rest (left, bold line), $p_{ET}O_2$ @AT (middle, - -) and $p_{a-ET}O_2$ (right, bold line). All pressures in mm Hg, error bars indicating 1 SD.

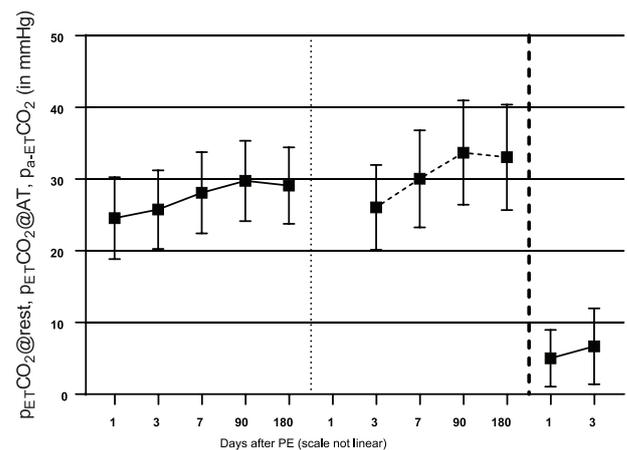


Figure 4. Carbon dioxide exchange. $p_{ET}CO_2$ @rest (left, bold line), $p_{ET}CO_2$ @AT (middle, - -) and $p_{a-ET}CO_2$ (right, bold line). All pressures in mmHg, error bars indicating 1 SD.

correlation with RV_{sys} at 6 months ($r^2 = 0.02$; $P = .5$ and $r^2 = 0.01$; $P = 0.8$ for $p_{(c-ET)}CO_2$ and $p_{(c-ET)}O_2$, respectively). At day 3, correlations remained weak and not significant for V'_E/V'_{CO_2} @AT ($r^2 = 0.01$; $P = .9$), V'_D/V'_T ($r^2 = 0.04$; $P = .3$), $p_{(c-ET)}CO_2$ ($r^2 = 0.04$; $P = .3$) and $p_{(c-ET)}O_2$ ($r^2 = 0.1$ [negative r];

$P = .8$). RV_{sys} at day 7 ($r^2 = 0.28$; $P = .03$) and at 3 months ($r^2 = 0.39$; $P < .01$) correlated with RV_{sys} at 6 months. There were weak correlations in late follow-up between RV_{sys} and V'_E/V'_{CO_2} @AT (at 6 months, $r^2 = 0.35$; $P < .01$) and RVEDd

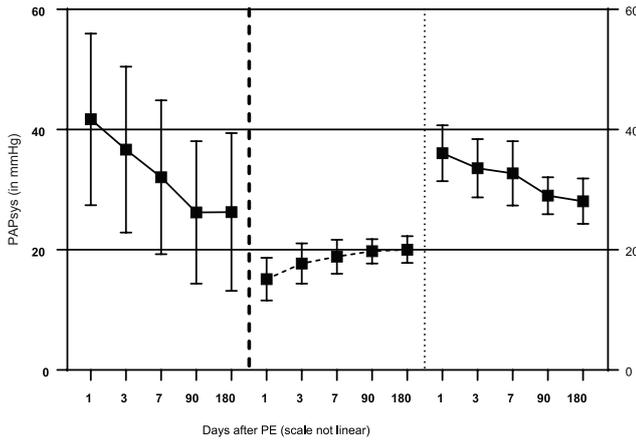


Figure 5. Right ventricular function. PAP_{sys} (left, bold line, in mmHg), TAPSE (middle, - -, in mm), RVEDd (right, bold line, in mm). Error bars indicating 1 SD.

(at 3 and 6 months, $r^2 = 0.27$ to 0.42 ; all $P < .02$). No other parameters were correlated with 6-month RV_{sys} . Detailed correlation data for all these parameters and for HR, oxygen pulse, peak V'_{O_2} , peak V'_{O_2} %predicted, V'_D/V'_T , and peak V'_E are summarized in supplementary Table 4.

Discussion

This study evaluated multiple parameters and their change over time after low- or intermediate-risk PE and searched for an association with RV_{sys} at 6 months after the embolic event. We confirmed our primary hypothesis that the V'_E/V'_{CO_2} slope (assessed at day 3 and 7) correlated with RV_{sys} half a year later. Clinical data, laboratory values or other parameters of gas exchange (secondary hypothesis, $V'_E/V'_{CO_2}@AT$, V'_D/V'_T , $p_{(c-ET)CO_2}$ and $p_{(c-ET)O_2}$) did not predict elevated RV_{sys} .

Since the landmark study by Riedel et al,³³ several attempts have been made to characterize the mismatch between ventilation and pulmonary perfusion in acute and chronic PE.^{23,24} Analysis of blood or respiratory gases alone does not predict the severity of PE, as shown for $p_{ET}CO_2$,¹⁶ $p_{(a-ET)O_2}$,³⁴ or capnography,¹⁹ and even a complex analysis of peak expiratory flow, minute ventilation, inspiration time and $p_{ET}CO_2$ reached a specificity of only 48%.¹⁵ Consistent with previous studies, we found RV_{sys} at 6 months to be correlated with neither V'_D/V'_T nor $p_{(a-ET)O_2}$ (both calculated from arterial and $p_{ET}O_2$). Only the V'_E/V'_{CO_2} slope was associated with estimated pulmonary pressure during follow-up. When obtained from standardized CPET at day 7, the calculation of the linear regression line V'_E versus V'_{CO_2} has a very low variance; by contrast, calculation of the V'_E/V'_{CO_2} slope from a bed-side test at day 3 is more variable and this correlation with RV_{sys} at 6 months just met significance. However, we demonstrated that this minimum in-bed effort led to metabolic changes large enough to determine the ventilatory response to carbon dioxide increase. In contrast to our findings, Held et al³⁴ found that $p_{(c-ET)CO_2}$ was the single parameter that best separated patients with CTEPH and controls, while McCabe et al²⁰ preferred

V'_D/V'_T . However, Held et al. evaluated patients with confirmed CTEPH and McCabe et al. patients with persistent pulmonary obstruction, that is, both studies assessed the very subgroup of patients that our study intended to select from all PE patients. In this respect, our results complement both studies and emphasize that CPET should be implemented far earlier. The excellent prognostic parameter peak V'_{O_2} could not be evaluated in our study, because a physical effort only 7 days after PE would probably remain at submaximum level. A recent study by Kahn et al³⁵ showed a close relation between impaired (ie, $<80\%$ of predicted value) peak V'_{O_2} at 1 month and at 1 year after PE. However, this study found no correlation of peak V'_{O_2} with systolic pulmonary arterial pressure (PAP_{sys}) or $V'_E/V'_{CO_2}@AT$ at 1 year, which might be due to the inclusion of only three patients with elevated PAP_{sys} and a completely normal $V'_E/V'_{CO_2}@AT$. Our differing predefined time points prevent a direct comparison with these results.

Compared with the measurement of gas exchange, echocardiography is still the preferred method for assessing RV dysfunction in PE. By use of echocardiography, Pengo et al² found that 12.5% of patients developed pulmonary hypertension (PH) at 6 months, and the proportion of patients with $RV_{sys} > 30$ mmHg in our study is in a comparable range (9.5%), though not verified invasively. Regarding echocardiographic parameters, a correlation with mortality has been shown for calculated RV_{sys} ,³⁶ while RV dilation and RV hypokinesia are associated with PE but failed to predict mortality in a large prospective study.³⁷ Lewczuk et al³⁸ found a high mortality of 38% at 4 years' follow-up in patients presenting with high pulmonary pressures at the time of the acute event, but this study used a higher cut-off level (*mean* pulmonary artery pressure > 30 mmHg) and obtained invasive hemodynamics. By contrast, our study estimated RV pressure non-invasively, investigated patients with a far lower risk of mortality and confirmed that at least RV_{sys} at day 7 could be a criterion for persistent PH. However, it is not clear that an elevated pulmonary pressure at this time should alter the therapeutic regimen. We believe that the complex interaction of hypocarbic bronchoconstriction, atelectasis, small peripheral embolism, inflammation, remodeling and RV dysfunction as described by Verschuren et al¹⁸ and Arbustini et al³⁹ cannot be reflected by a simple combination of the two parameters that were predictive in our study (V'_E/V'_{CO_2} slope and RV_{sys} at day 7). Nevertheless, both parameters are easy to obtain and reproducible and are in this respect more suitable as screening methods than invasive tests.

Plasma markers of RV strain such as troponin and BNP have been evaluated in acute embolism^{14,35} and in late follow-up.⁴⁰ However, the correlation between BNP and CTEPH as demonstrated by Klok et al⁴⁰ referred to a very late follow-up, a median of 4.5 years after the embolic event. Therefore, the missing correlation between BNP and RV pressure at 6 months in our study might be due to the limited number of patients, but may also indicate that BNP is not sensitive in early follow-up.

Limitations

Our study is limited by the small number of patients. Moreover, the measurement of the RV_{sys} was not validated by right heart catheterization, but this was necessary to keep the study design feasible. Further limitations arise from the blood gas analysis that was taken at rest only, so that the potentially interesting arterio-alveolar differences ($p_{(a-ET)O_2}$ and $p_{(a-ET)CO_2}$) at exercise are not available. A further difference to literature is the use of arterial blood gases at days 1 and 3 in our study; however, these are known to correspond to capillary gases, as demonstrated by Scheidl et al.²¹

Summary

The V'_E/V'_{CO_2} slope assessed at 3 or 7 days after acute PE is significantly correlated with the RV_{sys} (calculated by echocardiography) at 6 months after the acute event. Within this first week after PE, neither laboratory values nor gas exchange ($p_{(a-ET)CO_2}$, $p_{(a-ET)O_2}$, V'_D/V'_T) were related to RV_{sys} after 6 months. CPET with calculation of the V'_E/V'_{CO_2} slope may identify patients at risk of developing CTEPH as early as 7 days following acute PE.

Authors' Note

None of the authors have a financial or personal relationship with other people or organizations that could have influenced this study.

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