Prognostic value of the ECG on admission in patients with acute major pulmonary embolism

A. Geibel*, M. Zehender*, W. Kasper#, M. Olschewski¶, C. Klima* and S.V. Konstantinides+

ABSTRACT: A number of ECG abnormalities can be observed in the acute phase of pulmonary embolism (PE). Their prognostic value has not yet been systematically studied in large patient populations.

In 508 patients with acute major PE derived from a large prospective registry, the current authors assessed, on admission, the impact of specific pathological ECG findings on early (30-day) mortality.

Atrial arrhythmias, complete right bundle branch block, peripheral low voltage, pseudoinfarction pattern (Q waves) in leads III and aVF, and ST segment changes (elevation or depression) over the left precordial leads, were all significantly more frequent in patients with a fatal outcome. Overall, 29% of the patients who exhibited at least one of these abnormalities on admission did not survive to hospital discharge, as opposed to only 11% of the patients without a pathological 12-lead ECG. Multivariate analysis revealed that the presence of at least one of the above ECG findings was, besides haemodynamic instability, syncope and pre-existing chronic pulmonary disease, a significant independent predictor of outcome.

In conclusion, ECG may be a useful, simple, non-costly tool for initial risk stratification of patients with acute major pulmonary embolism.

KEYWORDS: Mortality, prognosis, pulmonary arterial hypertension, pulmonary embolism, pulmonary embolism diagnosis

AFFILIATIONS
*Dept of Cardiology and Angiology, Albert Ludwigs University of Freiburg, and
¶Institute for Medical Biometry and Statistics, University of Freiburg, Freiburg, and
#Dept of Internal Medicine, St. Josefs Hospital, Wiesbaden, and
+Dept of Cardiology and Pulmonary Medicine, Georg August University of Goettingen, Goettingen, Germany.

CORRESPONDENCE
S.V. Konstantinides
Georg August University of Goettingen
Dept of Cardiology and Pulmonary Medicine
Robert Koch Strasse 40
Goettingen D-37085
Germany
Fax: 49 5513914131
E-mail: skonstan@med.
uni-goettingen.de

Early identification of high-risk patients with acute pulmonary embolism (PE) remains a challenge in clinical practice [1]. It has been argued that development of right ventricular dysfunction as a result of acute pulmonary hypertension (PH) is a crucial pathophysiological event, which may initiate a vicious circle of progressive haemodynamic instability [2]. In accordance with this hypothesis, it is presently acknowledged that overt right ventricular failure with persistent arterial hypotension or shock predicts a particularly poor outcome and, thus, should set the indication for immediate thrombolytic, interventional or surgical treatment of PE [3, 4]. Furthermore, and importantly, a number of prospective [5–7] and retrospective [8] studies, as well as two large registries [1, 9], have demonstrated that echocardiographic diagnosis of right ventricular enlargement or hypokinesis [10] is associated with an increased risk of death or potentially life-threatening complications, even in the absence of arterial hypotension on admission. Accordingly, in a recent large randomised

trial, echocardiographic parameters were used to randomise patients to early thrombolytic treatment or heparin alone [11]. However, availability of cardiac ultrasound on a round-the-clock basis may pose significant logistical problems in several hospitals, and echocardiography may be of poor quality in overweight or mechanically ventilated patients, or in those with chronic pulmonary disease.

A number of studies suggest that cardiac biomarkers, and cardiac troponins and natriuretic peptides, may represent an important step towards reliable risk stratification of patients with PE [12]. More recently, it was reported that right ventricular enlargement based on reconstructed four-chamber views of the heart on chest computed tomography (CT; newer-generation, multidetector-row scanners) may also indicate potentially life-threatening PE [13]. However, while the prognostic value of novel laboratory markers and imaging modalities is being evaluated, it remains unknown whether triage of

patients with acute PE could become faster and easier if it included a simple, ubiquitously available, generally comprehensible and non-costly baseline test, such as the 12-lead ECG. In fact, it has been known for many years that a number of (usually transient) ECG abnormalities can be observed in the acute phase of PE [14], and some [15, 16], although not all [17], earlier studies suggested that these abnormalities might be related to the severity of PE. Conversely, the implications of specific pathological ECG findings with regard to the clinical outcome, and particularly the risk of death during the in-hospital phase, have not yet been systematically studied in a large population of consecutive patients with PE. In order to directly address this issue, the current authors analysed the data of a large prospective multicentre registry [1], investigating the prognostic value of specific ECG parameters on admission in 508 patients with acute major PE.

METHODS
Study protocol
The rationale, study protocol and inclusion criteria of the Management Strategy and Prognosis in Pulmonary Embolism Registry have been described previously [1, 18]. Briefly, 204 participating centres throughout Germany prospectively registered a total of 1,001 consecutive patients in whom the diagnosis of major (*i.e.* submassive or massive) PE was made according to predefined criteria. The inclusion criteria of the registry consisted of the following findings signifying right ventricular dysfunction and/or PH caused by PE: 1) arterial hypotension (systolic blood pressure <90 mmHg or a pressure drop of ≥40 mmHg for >15 min, if not caused by new-onset arrhythmia, hypovolaemia, or sepsis); 2) cardiogenic shock (arterial hypotension as defined previously accompanied by clinical signs of organ perfusion and hypoxia); 3) circulatory collapse with need for cardiopulmonary resuscitation; 4) echocardiographic findings indicating right ventricular pressure overload and/or PH (right ventricular dilatation, paradoxical septal wall motion, loss of inspiratory collapse of the inferior vena cava, or tricuspid regurgitation jet velocity >2.8 m·s^{-1} or <2.5 m·s^{-1} in the absence of inspiratory collapse of the inferior vena cava) without evidence of mitral valve disease or left ventriclar dysfunction; and 5) diagnosis of precapillary PH (mean pulmonary artery pressure >20 mmHg in the presence of normal pulmonary artery occlusion pressures) by catheterisation of the right side of the heart.

For inclusion in the registry, patients had to have clinical suspicion of PE [1] and fulfil at least one of the above criteria at presentation. Patients in whom PE was an accidental finding and not the primary clinical diagnosis on admission were excluded. Confirmation of venous thromboembolism by imaging studies (pulmonary angiography, ventilation–perfusion lung scan, and leg ultrasound or phlebography) was recommended in agreement with guidelines existing at the time the registry was established [19, 20]. The steering committee of the registry did not dictate specific management strategies to the participating centres and physicians.

The present study considered for statistical evaluation those registry patients who presented with acute symptom onset, *i.e.* those who were admitted to the hospital within 48 h after suffering symptoms related to PE, and who had a complete 12-lead ECG registration.

Data acquisition
Using a standardised questionnaire, complete information was obtained on: 1) the clinical symptoms and signs of the patients on admission; 2) the presence of underlying diseases or predisposing factors for venous thromboembolism; 3) the findings of all diagnostic procedures performed, including the original 12-lead ECG and the echocardiogram; 4) the treatment given to the patients (*e.g.* thrombolysis or heparin alone); and 5) the patients' clinical course (duration of hospital stay, causes of death for patients who died during the first 30 days after admission, major bleeding or other cardiovascular complications, and clinically apparent recurrence of PE as diagnosed by the on-site clinical investigator).

Original ECG tracings were sent to the coordinating centre (University of Freiburg, Freiburg, Germany) and analysed independently by two experienced cardiologists (A. Geibel and C. Klima) who were unaware of the patients' history and outcome. The following ECG abnormalities were regarded as suggestive of right ventricular overload [15, 21] and evaluated with regard to their impact on in-hospital mortality: 1) sinus tachycardia (>100 beats·min^{-1}) or bradycardia (<60 beats·min^{-1}); 2) atrial arrhythmias; 3) atrioventricular conduction abnormalities; 4) abnormal axis pattern (S1Q3T3 pattern, *i.e.* S waves in lead I and Q waves in lead III with T-wave inversion in III); 5) shift in the transition zone (R=S) to V5 or further leftward; 6) complete or incomplete right bundle branch block (RBBB); 7) peripheral low voltage (in the limb leads); 8) pseudo-infarction pattern (prominent Q waves) in leads III and aVF; 9) ST segment elevation ≥0.1 mV over the right (V2–V3) or the left (V4–V6) precordial leads; 10) ST segment depression ≥0.05 mV over the right or the left precordial leads; and 11) T-wave inversion over the right or the left precordial leads.

Statistical analysis
The prognostic relevance of ECG and other important baseline parameters with respect to in-hospital mortality was analysed univariately using Fisher's exact test. To additionally define the role of ECG and that of clinical and echocardiographic findings as determinants of outcome, a multiple logistical regression model was applied to the end point of overall mortality, taking into account those variables that reached a p-value <0.20 in the univariate comparison. The results of the logistical regression model are presented as estimated odds ratios with the corresponding 95% confidence intervals. All significance tests were two-sided.

RESULTS
Diagnosis, treatment and in-hospital clinical course
In total, 508 patients were analysed, 294 females and 214 males, with a mean±SD age of 63±15 yrs (range 17–92 yrs). As part of the diagnostic workup on admission, a high-probability lung scan was obtained in 270 patients (53%), and pulmonary angiography was performed in 84 patients (17%), confirming the presence of pulmonary thromboembolic obstruction in all cases. In addition, the diagnosis of deep venous thrombosis was established in 358 of the patients (70%) studied by vein sonography or phlebography. Overall, 469 study patients (92%) had confirmation of venous thromboembolism by at least one of these imaging studies. In the remaining patients, whose clinical and haemodynamic condition was considered

too critical to permit transportation from the emergency room or intensive care unit, the diagnosis of acute (massive) PE was based on clinical probability combined with bedside transthoracic echocardiography, if the latter indicated PH and/or acute right ventricular pressure overload in the absence of left ventricular or mitral valve disease [1].

A complete echocardiographic examination was available in 348 patients (69%), and revealed the presence of right ventricular pressure overload and/or PH in 306 patients (88%). Furthermore, 133 patients (26%) underwent catheterisation of the right side of the heart, which disclosed the presence of precapillary PH in 88% of the cases.

After diagnosis of major PE, 204 patients (40%) received thrombolytic treatment within the first 24 h. The remaining 304 patients initially underwent conventional heparin anticoagulation. Of these patients, 41 (13%) underwent thrombolytic treatment by the attending physicians later during the hospital stay (*i.e.* after the first 24 h).

The mean duration of hospital stay after diagnosis of major PE was 19.7 ± 15.9 days. Overall 30-day mortality was 23%, and death was directly related to the pulmonary thromboembolic event in almost all cases (116 of 118 deaths; 98%). Recurrence of PE was reported in 79 patients (16%).

Clinical, echocardiographic and ECG findings on admission: correlation with patient outcome

The clinical characteristics of the patients at the time of diagnosis are summarised in table 1. The mean age of the patients who survived to hospital discharge was 61.9 ± 15.4 yrs compared with 66.8 ± 13.1 yrs in those who died (p=0.002). There were no differences between survivors and nonsuvivors, with regard to the history of recent surgery or major trauma, previous venous thrombosis or PE, cancer, stroke or pregnancy. Conversely, arterial hypotension or shock, syncope, and history of chronic cardiac or pulmonary disease were all significantly associated with a higher death rate (table 1).

TABLE 2	Relationship of ECG abnormalities on admission to the outcome of patients with acute pulmonary embolism

Parameter	Survivors	Nonsurvivors	p-value
Subjects n	390	118	
Sinus tachycardia >100 beats·min⁻¹	261 (67)	87 (77)	0.063
Atrial arrhythmia	46 (12)	29 (25)	0.001
Abnormal axis pattern#	85 (22)	29 (25)	0.53
Shift in the transition zone to V5	138 (35)	51 (43)	0.13
Complete RBBB	51 (14)	33 (29)	<0.001
Incomplete RBBB	74 (19)	14 (12)	0.53
Peripheral low voltage	84 (22)	41 (35)	0.005
Q in leads III and aVF, but not in II	28 (7.2)	16 (14)	0.039
ST elevation in leads I, II, V4–V6	22 (5.8)	18 (16)	0.001
ST depression in leads I, II, V4–V6	142 (38)	56 (49)	0.030
T-wave inversion in leads V2–V3	194 (50)	52 (44)	0.39
T-wave inversion in leads V4–V6	128 (34)	48 (42)	0.12

Data are presented as n (%), unless otherwise stated. RBBB: right bundle branch block. #: S1Q3T3.

Dilatation of the right ventricle (*i.e.* right ventricle appearing larger than the left ventricle from the apical or subcostal view, or right ventricular end-diastolic diameter >30 mm from the parasternal view) was detected in 259 of the 348 patients (74%) who underwent echocardiography. In these patients 30-day mortality was 25% as opposed to 13% in those without a dilated right ventricle (p=0.016).

The 12-lead ECG also exhibited significant differences between survivors and the nonsurvivors during the first 30 days after admission. As shown in table 2, atrial arrhythmias (mostly atrial fibrillation or flutter), complete RBBB, peripheral low voltage, pseudoinfarction pattern (Q waves) in leads III and

TABLE 1	Association between baseline clinical characteristics and 30-day mortality

Clinical characteristics at diagnosis	Survivors	Nonsurvivors	p-value
Subjects n	390	118	
Age >65 yrs	193 (49)	71 (60)	0.046
Females/males (ratio)	225/165 (1.4:1)	69/49 (1.4:1)	0.92
Syncope	140 (36)	66 (56)	<0.001
Arterial hypotension	226 (58)	101 (86)	<0.0001
Recent major surgery#	55 (14)	15 (13)	0.76
Major trauma or fracture#	12 (3.1)	5 (4.2)	0.56
History of venous thrombosis	114 (29)	33 (28)	0.82
History of pulmonary embolism	49 (13)	13 (11)	0.75
History of cardiac disease	112 (29)	45 (38)	0.05
Chronic pulmonary disease	31 (8.0)	20 (17)	0.008
Cancer	44 (11)	19 (16)	0.20
History of stroke	17 (4.4)	8 (6.8)	0.33
Gestation	12 (5.3)	1 (1.5)	0.31

Data are presented as n (%), unless otherwise stated. Arterial hypotension was defined as systolic blood pressure <90 mmHg, or a pressure drop of ⩾40 mmHg for at least 15 min, if not caused by new-onset arrhythmia, hypovolaemia or sepsis. #: within 10 days.

aVF, and ST segment changes (elevation or depression) over the left precordial leads were all significantly more frequent in patients with a fatal outcome. Overall, 29% of the patients who exhibited at least one of these abnormalities on admission did not survive to hospital discharge, as opposed to only 11% of the patients without a pathological 12-lead ECG (p<0.001). This difference yielded a positive predictive value of 29% and a negative predictive value of 84% with respect to 30-day mortality. In addition, there appeared to be a tendency towards a correlation between a pathological ECG and the dysfunction (dilatation) of the right ventricle on the initial echocardiogram. Overall, 78% of the current patients who exhibited at least one of the ECG findings mentioned previously also had an abnormal echocardiogram, compared with 68% of those without a pathological ECG (p=0.068).

The calculated prognostic sensitivity and specificity, as well as the negative and positive predictive value, of each one of the ECG parameters, which were univariately associated with an adverse outcome (p<0.05), are displayed in table 3. When examined by multiple logistical regression analysis (data not shown), none of these ECG abnormalities (atrial arrhythmias, complete RBBB, peripheral low voltage, Q in leads III and aVF but not in II, or ST elevation or depression in leads I, II, V4–6) was individually associated with a poor outcome after adjustment for the patients' clinical symptoms and findings on admission, and for the presence of pre-existing pulmonary and cardiac disease. However, multivariate analysis (table 4) revealed that the presence of at least one of these findings was, besides haemodynamic instability, syncope and chronic pulmonary disease, a significant independent predictor of outcome.

DISCUSSION

Since the 1970s, a number of carefully designed cohort studies [22–25], registries [1, 9, 26] and prospective randomised therapeutic trials [27, 28] have substantially improved understanding of the clinical course and prognosis of acute PE. At present, more than 30 yrs after the experimental studies of McIntyre and Sasahara [29, 30] on the haemodynamic response to pulmonary vascular obstruction, right ventricular dysfunction and failure is widely accepted to be the single most important determinant of outcome in the acute phase of venous thromboembolism. Accordingly, the prognostic value

TABLE 4	Predictors of 30-day mortality in patients with acute major pulmonary embolism	
Clinical characteristics	**Odds ratio (95% CI)**	**p-value**
Age >65 yrs	1.21 (0.77–1.93)	0.39
Arterial hypotension	3.55 (2.04–6.48)	<0.001
Syncope	1.63 (1.04–2.55)	0.032
Chronic pulmonary disease	2.11 (1.08–4.07)	0.026
Abnormal ECG[#]	2.56 (1.49–4.57)	<0.001

CI: confidence interval. [#]: at least one of the following ECG findings on admission (also shown in table 3): atrial arrhythmia; complete right bundle branch block; peripheral low voltage; Q in leads III and aVF, but not in II; ST elevation in leads I, II, V4–6; and ST depression in leads I, II, V4–6.

of echocardiographic and, more recently, CT imaging in patients with suspected PE lies primarily in the detection of right ventricular dilatation and/or hypokinesis [10, 13, 31, 32]. However, it has never been directly tested in a large patient population whether risk assessment based on acute right heart strain might also be possible using a simple baseline test, such as the 12-lead ECG. This hypothesis appears to be supported by a number of earlier and more recent reports, which suggested that specific ECG changes may correlate with the severity of PE [15, 16, 33].

The present study was based on the population of a large prospective multicentre registry [1], which investigated management strategies and the prognosis of acute PE. As with a previous large thrombolysis trial, the current study focused on patients with submassive and massive PR, i.e. patients at a particularly high risk of death or major cardiovascular complications during the hospital stay [34]. However, rather than attempting to correlate the ECG abnormalities with angiographic, haemodynamic or scintigraphic findings indicating severe PE [15, 16, 33], the present study directly examined the prognostic relevance of the 12-lead ECG with regard to 30-day mortality. Univariate analysis of the large study population (n=508) suggested that a number of ECG changes on admission, including atrial arrhythmias, complete RBBB, peripheral low voltage, and ST segment changes (elevation or depression) over the left precordial leads, were significantly associated with an adverse clinical outcome. Thus, the ECG abnormalities that were reported in earlier studies [15, 35] to indicate severe PE also appeared to affect prognosis in the present study, although the current authors could not confirm the prognostic relevance of the anterior subepicardial ischaemic pattern indicated by T-wave inversion over leads V1–V4 [16]. In addition, there appeared to be a tendency towards a correlation between a pathological ECG (defined as at least one of the above abnormalities) and the echocardiographic detection of right ventricular dilatation, a reliable marker of overt or impending right ventricular failure and an established predictor of in-hospital outcome [5, 31]. When examined by multivariate analysis, none of the ECG abnormalities was individually associated with a poor outcome after adjustment for the patients' clinical symptoms and findings on admission, and for the presence of pre-existing pulmonary and cardiac disease. However, multiple logistical

TABLE 3	Prognostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of ECG findings with regard to 30-day mortality			
Parameter	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Atrial arrhythmia	25	88	39	79
Complete RBBB	29	87	39	80
Peripheral low voltage	35	79	33	81
Q in leads III and aVF, but not in II	14	93	36	78
ST elevation I, II, V4–V6	16	94	41	79
ST depression I, II, V4–V6	49	62	28	81

Data are presented as %. RBBB: right bundle branch block.

regression revealed that the presence of at least one of these findings was, besides haemodynamic instability, syncope and chronic pulmonary disease, a significant independent predictor of early death.

The physiological basis for the ECG findings associated with PE still remains difficult to define. Although it was suggested as early as 1938 that the ECG might reflect the development of right ventricular distention [14], this association now seems to be much more complex than initially thought. In particular, the appearance and the temporal pattern of ECG changes did not reliably correlate with the appearance and resolution of PH or of echocardiographically diagnosed right ventricular enlargement in subsequent reports [16, 17] and in the present study. Furthermore, although it is appealing to assume that the ECG findings in PE are the result of myocardial ischaemia and/or right ventricular wall stress, studies using scintigraphic and enzymatic (creatine kinase) assessment have not been able to demonstrate evidence of ischaemia in patients with T-wave changes over the anterior precordial leads [13].

In conclusion, in a large population of 508 patients with acute major pulmonary embolism, the present study demonstrated that the presence of at least one prespecified ECG abnormality on admission was, apart from the clinical findings at presentation, a predictor of outcome in the acute phase. Thus, the present results support the notion that the ECG may be useful as a simple, non-costly initial tool for assessing the patients' prognosis and for guiding further diagnostic work-up and therapeutic decisions in clinical practice. This aspect may also have to be considered when designing future studies to evaluate the prognostic value and, particularly, the therapeutic implications of novel laboratory markers and/or radiological modalities in patients with acute major pulmonary embolism.

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