REVIEW ARTICLE

The Value of Electrocardiographic Abnormalities in the Prognosis of Pulmonary Embolism: A Consensus Paper

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Electrocardiographic (ECG) abnormalities in the setting of acute pulmonary embolism (PE) are being increasingly characterized and mounting evidence suggests that ECG plays a valuable role in prognostication for PE. We review the historical 21-point ECG prognostic score for the severity of PE and examine the updated evidence surrounding the utility of ECG abnormalities in prognostication for severity of acute PE. We performed a literature search of MEDLINE, EMBASE, and PubMed up to February 2015. Article titles and abstracts were screened, and articles were included if they were observational studies that used a surface 12-lead ECG as the instrument for measurement, a diagnosis of PE was confirmed by imaging, arteriography or autopsy, and analysis of prognostic outcomes was performed. Thirty-six articles met our inclusion criteria. We review the prognostic value of ECG abnormalities included in the 21-point ECG score, including new evidence that has arisen since the time of its publication. We also discuss the potential prognostic value of several ECG abnormalities with newly identified prognostic value in the setting of acute PE.

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Acute pulmonary embolism (PE) is a frequent cause of cardiovascular morbidity and mortality. Timely diagnosis of PE can be challenging and many deaths from PE occur prior to diagnosis.¹ With improved diagnostic modalities, overall mortality for PE has improved to 12%,² but for the subgroup of patients who present with massive PE, mortality can be as high as 52%.³ Risk factors for PE

are well described and include: recent surgery or immobility, malignancy, infection, pregnancy, oral contraceptive use, hormonal replacement therapy, smoking, among others.^{4–7} Several negative physiologic consequences occur due to PE and ultimately can lead to right ventricular (RV) failure as the primary cause of death in severe PE.⁸

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The European Society of Cardiology (ESC) recently published a guideline on the diagnosis and management of acute PE.⁸ In this guideline, several diagnostic modalities are carefully discussed in terms of their value in assisting with diagnosis of PE. These include: D-dimer measurement, computed tomographic pulmonary angiography (CTPA), lung scintigraphy, pulmonary angiography, magnetic resonance angiography, echocardiography, and compression venous ultrasonography. The utility of various clinical tools in prognostication is also assessed and it is recommended that this occur via clinical parameters, such as, hemodynamics, imaging of the RV by echocardiogram or CTPA, laboratory biomarkers (e.g., BNP, NT-proBNP, Troponin), and various assessment scores, such as the Pulmonary Embolism Severity Index (PESI).⁸

Of notable absence in the clinical tools for prognostication in the ESC guideline is the role for electrocardiography (ECG). Though reference is made to potential ECG changes in PE, the relative value of ECG is underreported and is not listed in the recommended modalities suggested to assist with prognostic assessment of acute PE. ECG is one of the first tests to be performed in the emergency department when a patient presents with cardiac or respiratory symptoms.⁹ It is a rapidly interpretable, noninvasive test with minimal associated risk or cost, and it is available in remote areas where modern technology may not be. While no isolated ECG abnormality is definitively associated with PE, certain constellations of ECG abnormalities have been shown to be reasonably specific.¹⁰⁻¹³ ECG abnormalities in PE are being increasingly reported and characterized.^{11, 14-20} Furthermore, mounting evidence suggests that ECG plays a valuable role in prognostication for PE, with various ECG abnormalities having been demonstrated to be reasonable predictors of hemodynamic decompensation,²⁰ RV dysfunction (RVD),²¹ elevated mean pulmonary artery pressure (MPAP),²² in-hospital complication,^{17, 23, 24} cardiogenic shock,¹⁸ and even mortality.^{14, 23, 25, 26} As such, a consensus paper on the role of ECG in the prognostication of PE is both timely and necessary.

We review an historical ECG prognostic score for the severity of PE and examine the updated evidence surrounding the utility of ECG abnormalities in prognostication for severity of acute PE, both in terms of previously well-documented ECG abnormalities, as well as signs whose prognostic

roles in PE have been newly recognized. We highlight the need for a revised scoring system that could assist with predicting outcome and severity of PE, particularly when modern technology may not be readily accessible.

METHODS

We searched MEDLINE, EMBASE, and PubMed up to February 2015 using keywords and MeSH terms including: "electrocardiography," "ECG," "PE," "S1Q3T3," "T-wave inversion (TWI)," "ST elevation (STE)," "ST depression," "bundle branch block," "long QT interval," "low voltage," "atrial arrhythmia," "prognosis," "mortality," and "outcomes." The search was limited to humans and articles in the English language. Case reports were excluded, but case series and observational studies were included. Article titles and abstracts were screened, and articles were included if a surface 12-lead ECG was used as the instrument for measurement, a diagnosis of PE was confirmed by imaging, arteriography or autopsy, and analysis of prognostic outcomes was performed (e.g., mortality, cardiogenic shock, in-hospital complication, hemodynamic deterioration, etc.). Further articles were found from the reference lists of the selected articles as well as from the review articles that were found with the initial search, and were assessed for inclusion based on the same requirements.

PATHOPHYSIOLOGY OF PE LEADING TO ECG CHANGES

Acute PE has severe physiologic consequences including interference in gas exchange and circulation. Gas exchange abnormalities relate to the release of inflammatory mediators resulting in surfactant dysfunction, atelectasis and functional intrapulmonary shunting.²⁷ Circulatory changes originate from PE-induced vasoconstriction due to inflammatory mediators and hypoxia, which contributes to the initial increase in pulmonary vascular resistance (PVR).²⁸ Mechanical obstruction from thrombus can further increase pulmonary artery pressure and PVR. Abrupt increase in PVR leads to RV dilation and alteration of contractile properties of the RV myocardium. This results in inotropic and chronotropic stimulation as a compensatory mechanism. RV contraction time becomes prolonged and can lead to leftward

bowing of the interventricular septum.²⁹ The desynchronization of the ventricles may be exacerbated by development of right bundle branch block (RBBB) leading to impaired LV filling and systemic hypotension.³⁰ RV ischemia can occur as a consequence of the increased demand.

The summary of these pathophysiologic consequences contributes to the ECG changes associated with PE and may become manifested by depolarization abnormalities (e.g., RBBB) and repolarization abnormalities (e.g., ST-segment elevation, ST-segment depression, negative T waves) as well as atrial arrhythmias, or a combination of abnormalities. In fact, among patients with PE and RVD on admission, over 50% demonstrated at least one ECG sign of RV strain in a frequency that was sixfold more frequent than in the group with no RVD.²¹ Tayama et al. report that more than two abnormal ECG findings were observed in 71.4% of patients with acute massive or submassive PE and concluded that ECG is a useful tool for diagnosis of acute PE.³¹ Furthermore, an ECG with at least one abnormality known to be associated with PE was found to have an OR of 2.56 for predicting 30-day mortality in patients with acute major PE, highlighting the potential prognostic value of ECG findings.¹⁴ Herein, we review the evidence for an historical prognostication score for severity of PE, and we also review recent findings in the utility of ECG abnormalities in the prognostic assessment of PE.

HISTORICAL PROGNOSTIC SCORES FOR PE

Several clinical scores have been developed to estimate severity of PE. These include the Geneva Score, which includes clinical and patient factors such as cancer, heart failure, previous deep vein thrombosis (DVT), hypotension, low arterial oxygenation, and presence of DVT on ultrasound to predict an adverse outcome.³² Since then, the PESI score was developed with both an original and simplified version, and includes parameters, such as, cancer, heart failure, chronic pulmonary disease, tachycardia, hypotension, and hypoxemia to predict 30-day mortality.^{33,34} The PESI score is recommended in the ESC guideline for the diagnosis and management of PE on the basis of the score's ability to accurately classify patients according to risk of adverse outcome.⁸

Notably, aside from tachycardia, neither of these scoring systems utilizes any ECG abnormalities to assist with prognostication, despite many studies suggesting a potential role for ECG in this regard.

In order to address this, Daniel et al. developed an ECG scoring system in 2001 that they hypothesized would vary in proportion to the severity of pulmonary hypertension in PE and would help to distinguish patients with massive PE from patients with smaller PE or without PE.¹³ They created a 21-point ECG scoring system, whereby points were assigned for the following ECG abnormalities (number of points assigned in brackets): sinus tachycardia (2), incomplete RBBB (2), complete RBBB (3), TWI in leads V₁–V₄ (0–12), S wave in lead I (0), Q wave in lead III (1), inverted T in lead III (1), and entire S1Q3T3 complex (2). The scoring system was derived by aggregating data from four prior studies (two from the 1970's and two from the 1990's) in which a total of 239 patients had either massive or submassive PE.^{11,35–37} The data were then used to rank the frequency of major abnormalities associated with PE. The scoring system was validated using ECGs obtained within 48 hours prior to pulmonary arteriography for 60 patients (26 with PE, 34 without PE) and 25 patients with fatal PE. They found that the scoring system showed a significant positive relationship to systolic pulmonary arterial pressure (sPAP) in patients with PE ($r = 0.387$, $P < 0.001$), and that only patients with severe pulmonary hypertension from PE had a significantly higher ECG score. At a cutoff of 10 points, the ECG score was 23.5% sensitive and 97.7% specific for the recognition of severe pulmonary hypertension (sPAP > 50 mmHg).

Since then, other studies have attempted to use Daniel et al.'s 21-point ECG score in prognostication for PE severity. Kostrubiec et al. assessed whether the ECG score would be useful for risk stratification during hospitalization. They identified that patients with in-hospital complications had higher ECG scores compared to patients with an uneventful course (8 vs 3, $P = 0.04$).³⁸ They also found that higher ECG scores were found in patients with RVD versus those without (8 vs 2, $P = 0.004$) and that a score ≤ 3 could exclude RVD with high probability.³⁸ Since then, Golpe et al. found that the ECG score correlated significantly with the clot load score ($r = 0.41$, $P < 0.001$), systolic pulmonary artery pressure ($r = 0.31$, $P = 0.006$), pulmonary artery diameter

($r = 0.28$, $P = 0.011$), and right ventricle to left ventricle ratio measured by echocardiography and CTPA ($r = 0.42$, $P = 0.001$; and $r = 0.36$, $P = 0.004$, respectively).³⁹ Meanwhile, Subramaniam et al. found no correlation between ECG score and mean clot burden ($r = 0.09$, $P = 0.39$), or 12-month mortality, with a score of 2.4 for patients who survived compared to 2.03 for patients who died ($P = \text{NS}$).⁴⁰ Finally, Toosi et al. used Daniel's 21-point ECG score to compare the presence of RVD with the end points of complicated in-hospital course or death. They found that the ECG score was higher in patients with RVD ($P < 0.001$) and a complicated in-hospital course ($P < 0.05$), but that the ECG score was not significantly different in nonsurvivors.⁴¹ Based on their results, they concluded that the 21-point ECG scoring system could predict RVD in patients with acute PE well, but that its ability to predict an adverse in-hospital course was limited due to overall score operating characteristics.

Since then, there have been attempts to combine the 21-point ECG score with clinical features to improve the score's operating characteristics. Bircan et al. combined the ECG scoring system with arterial blood gas (ABG) analysis and shock index in predicting severe PE and found that the combination of scores enhanced the specificity of the ECG score in predicting RVD or severe PE patients (73.7% combined score vs 52.6% 21-point ECG alone), at the expense of sensitivity (58.8% combined score vs 70.6% ECG alone).⁴² Another study by Kline et al. found that a panel of tests including pulse oximetry, ECG score, and serum troponin measurement had an overall prognostic utility that was equivalent to echocardiography for prediction of a poor outcome from PE in normotensive patients, though an ECG score >8 had the highest specificity and positive predictive value (100% each).⁴³

In recent years, there have been several studies that have provided further information on the utility of common ECG abnormalities in the prognostic assessment of PE. Furthermore, several previously unreported ECG phenomena are gaining attention for their potential value in PE, including QR in lead V₁, QRS fragmentation, STE in leads III, V₁ and aVR, among others. In light of this, a renewed assessment of the potential role for ECG in assessing severity of PE is needed. Herein, we summarize the updated evidence for the utility of various ECG signs as prognostic markers and

review the evidence for newly described ECG phenomena that have not previously been included in ECG scoring systems for prognostication.

UPDATED EVIDENCE ON THE VALUE OF ECG AS A PROGNOSTIC TOOL

ECG Abnormalities Included in 21-Point ECG Score

Sinus Tachycardia

The presence of sinus tachycardia on ECG in the setting of PE is worth two points in the Daniel et al. prognostic score,¹³ however there is mixed evidence regarding the prognostic role of sinus tachycardia in this setting.

Sinus tachycardia has been found to be more common in patients with RVD than those without RVD (50% vs 16%, $P = 0.012$; 55% vs 29%, $P < 0.05$; 58% vs 21%, $P = 0.002$),^{15,41,44} but was not found to be significant in multivariate logistic regression analysis,⁴⁴ and only a trend toward significance was found by Bircan et al. (69% vs 31%, $P = \text{NS}$).⁴² Sinus tachycardia has also been found to be more common in patients with RV enlargement than those without (29% vs 18%, $P = 0.02$).¹⁹ Furthermore, sinus tachycardia may be more common in patients with acute PE than chronic PE (74% vs 51%, $P = 0.007$),⁴⁵ as well as in pulmonary trunk embolism than peripheral embolism (100% vs 30%), though statistical significance was not calculated for the latter.⁴⁶

In terms of prognostication, sinus tachycardia has been shown to be more prevalent in patients with massive PE than nonmassive PE in one study (36% vs 0%),³⁷ but this finding was not replicated by Bircan et al.⁴² While some studies have shown that patients with sinus tachycardia are at increased risk of in-hospital complications (88% vs 19%, $P = 0.0003$; 65% vs 38%, $P < 0.05$)^{38,41} and in-hospital death (91% vs 37%, $P < 0.001$),⁴¹ several studies have found no significant association with either,^{23,38,45} nor with degree of cardiac biomarker elevation.⁴⁷

It appears as though more studies have assessed the prognostic role of atrial arrhythmias and tachycardia "not-further-specified" in the setting of PE rather than sinus tachycardia alone. These will be discussed below. Furthermore, when determining

the relative prognostic role of tachycardia in the setting of PE, it is important to consider that some patients are unable to mount a tachycardic response on the basis of older age, medications, or comorbid disease.

Right Bundle Branch Block (RBBB)

RBBB is an ECG sign of acute RV strain and dilation affects peripheral branches of the right bundle branch (Fig. 1A).^{21,46,48} The incidence of incomplete or complete RBBB in association with PE has been reported in many studies with a variable range from 6% to 69%^{11,37,48-51} with some overall estimates closer to 25%.⁴⁸ The presence of the RBBB pattern has been noted to be more frequent in cases of massive trunk obstruction than peripheral embolism,⁴⁶ which is likely the result of more significant RV overload. It is therefore not surprising that RBBB tends to appear in more severe cases of PE.

In fact, Zhan et al.²⁰ reported onset of RBBB in 30% of patients with PE who developed hemodynamic instability. Furthermore, in a case series by Yoshinaga et al.,²² patients that exhibited the finding of RBBB on ECG were more likely to have a MPAP ≥ 40 mmHg (75% of patients with RBBB), though the overall incidence of RBBB was relatively low (4 patients, 19%). In a larger observational study, complete or incomplete RBBB was more frequently observed in patients with RVD than in those without RVD (46% vs 15%, $P = 0.023$).¹⁵ This was confirmed by another group demonstrating RBBB in 35% of patients with RVD compared to 7% in those without RVD ($P = 0.007$).⁴⁴ Even in patients who are hemodynamically stable, the presence of RBBB was higher in patients with RVD compared to those without (15% vs 5%, $P = < 0.001$).²¹ In this study, the presence of one or more classic ECG signs of RV strain was associated with increased risk of death or clinical deterioration (HR 2.58).

In keeping with this finding, RBBB has been associated with mortality (28% vs 10%, $P = 0.004$; OR 2.73, $P = 0.026$)^{26,52} as well as in-hospital complication (22% vs 9%, $P = 0.002$; OR 2.25, $P = 0.018$).^{26,52} Meanwhile, another study found that complete RBBB was associated with higher mortality (14% survivors vs 29% nonsurvivors, $P < 0.001$), though incomplete RBBB was not.¹⁴

Despite this observation, incomplete or complete RBBB has been found to have an OR of 2.49 for

mortality ($P = 0.006$),²³ and complete RBBB has an OR of 2.46 for cardiogenic shock ($P = 0.004$),¹⁸ which remained significant in multivariate regression analysis as an independent predictor of cardiogenic shock. Despite several studies demonstrating an association between RBBB and mortality in PE, several other studies have found no significant association in this regard,^{24,25,38,42,45,53} while some studies have demonstrated a nonsignificant trend toward association with mortality (complete RBBB in 50% of nonsurvivors vs 31% of survivors, $P = \text{NS}$) and in-hospital complications (50% vs 29%, $P = \text{NS}$).^{38,54} Thus, the association of RBBB with mortality due to PE remains equivocal.

Furthermore, not all studies have found an association of RBBB with other measures of severity of PE. While positive cardiac biomarkers have been found in a greater proportion of patients with RBBB in the setting of PE, these results have not been statistically significant.^{16,47,53} Similarly, while more patients with PE and RV enlargement on CTPA exhibited incomplete or complete RBBB than those without RV enlargement, the result was not found to be significant.¹⁹ Finally, one study of syncope in PE found a greater proportion of patients with new incomplete RBBB in patients with syncope (18%) than without syncope (5%), but the result was nonsignificant.⁵⁵ Though these studies have demonstrated nonsignificant results, they demonstrate a trend toward an increased incidence of RBBB in more severe PE, and so the potential utility of RBBB as a prognostic indicator for severity of PE is still unclear.

Of interest, the finding of PE associated with RBBB is often transient in nature resolving within 3 months to 3 years.⁴⁹ This may be because RBBB is transiently associated with cor pulmonale⁵⁶ and that the PE-related RBBB pattern resolves with restoration of normal right-sided cardiac hemodynamic parameters.⁴⁸

Overall, typical RBBB morphology in lead V_1 is a frequent phenomenon in acute PE that contains prognostic significance.^{46,48} Though the sensitivity of both incomplete and complete RBBB is limited for overall PE, both have good specificity (99% and 97%, respectively)¹⁹ and appear to be more common in severe PE. Of interest, variations in QRS morphology have been reported that are thought to be associated with concealment of RBBB. Analysis of the QRS morphology in leads V_3R-V_5R in patients with a notched S wave in lead V_1 revealed that the majority showed

Figure 1. (A) ECG at time of acute pulmonary embolism depicting right bundle branch block, and ECG after thrombolytic therapy demonstrating resolution of right bundle branch block and development of T-wave inversion in V_1 – V_4 (reproduced from Kim et al.¹⁵ with permission from Korean Circulation Journal Copyright © 2009 The Korean Society of Cardiology). (B) ECG at time of presentation with acute pulmonary embolism demonstrating T-wave inversion in leads III and deep T-wave inversion in V_1 – V_3 (reproduced from Kosuge et al.²⁴ with permission from Circulation Journal, Japanese Circulation Society).

triphasic QRS morphology with final R' wave in QRS complexes in leads V_3R – V_5R .⁵⁷ This QRS morphology in association with a notched S wave in lead V_1 is suggestive of the possibility of concealed incomplete or complete RBBB. Zhan et al. demonstrated that in 18 of 20 patients with PE, new changes of QRS morphology in lead V_1 were noted after onset of hemodynamic stability, suggesting that the notched S wave in lead V_1 may be the early presentation of RBBB but also that the Qr sign may be a more severe ECG sign than RBBB.²⁰

T-Wave Inversion

Anterior Leads. TWI is a repolarization abnormality that has been frequently reported to be associated with PE (Figs. 1A and B). The pathophysiology of T-wave changes in the precordial leads is not well established, but is thought to be the consequence of an ischemic phenomenon due to low cardiac output in the context of RV dilation and strain.^{15,37,58} Presence of TWI in anterior leads has been reported with variable frequency

from 16% to 68%.^{21,50} This ECG abnormality makes up a significant component of the 21-point ECG score by Daniel et al. with up to 15 points being assigned based on presence and depth of TWI in leads V_1 – V_3 .¹³ Despite this, the evidence supporting the usefulness of this ECG phenomenon is contradictory with several studies showing prognostic significance and several others showing no significant value in this regard.

The potential association of TWI in precordial leads with poor prognosis in acute PE has been documented since the 1970's. Stein et al. found that TWI occurred in 46% of patients with massive PE and 38% of patients with submassive PE,³⁶ while McIntyre et al. found that precordial TWI was more likely if the PAP was >30 mmHg, though only two patients exhibited this ECG abnormality in their study.³⁵ Since then, a study in 1997 found that 81% of patients with acute PE and TWI in the anterior leads had a PAP >30 mmHg.³⁷

Several studies have found that patients with acute PE that exhibit the ECG finding of TWI in leads V_1 – V_3 are significantly more likely to have RVD (75% RVD+ vs 5% RVD–, $P < 0.001$;

23% RVD+ vs 7% RVD-, $P < 0.001$; 63% RVD+ vs 3% RVD-, $P < 0.0001$).^{15,21,44} In multivariate logistic regression analysis, TWI in V_1 - V_3 had an OR of 22.8 for predicting RVD and was the most significant ECG variable to be associated with RVD compared with S1Q3T3 and sinus tachycardia ($P = 0.007$).⁴⁴ Another group found an association between TWI in lead V_2 and RVD (45% RVD+ vs 6% RVD-, $P < 0.001$), with a specificity of 85% for RVD.⁵³ TWI in leads V_1 - V_4 was also found to be associated with abnormal RV contraction in patients with acute PE (31% abnormal vs 3% normal, $P \leq 0.001$), and TWI in each of leads V_1 - V_3 were also individually associated with abnormal RV contraction.⁴¹ Finally, though Bircan et al. did not find a significant association between RVD and TWI in any of leads V_1 - V_3 or all of leads V_1 - V_4 , there was a trend toward an association with RVD (TWI V_1 69% vs 31%, TWI V_2 , 78% vs 22%, TWI V_3 78% vs 22%, TWI V_1 - V_4 82% vs 18%),⁴² and lack of statistical significance may have been related to small sample size. Resolution of TWI in anterior leads has been correlated with recovery of RVD ($r = 0.84$, $P < 0.01$),^{15,44} and has been reported to occur in 22% of patients by day 5 or 6 postpulmonary angiography, and in 49% by day 14.³⁶

An association between TWI in precordial leads and positive cardiac biomarkers in the setting of acute PE has also been found. Patients with TWI in lead V_2 were significantly more likely to have a positive troponin than a normal troponin (48% vs 20%, $P = 0.03$),⁵³ and patients with TWI in leads V_2 - V_4 were also more likely to have a positive troponin (57% vs 27%, $P = 0.0001$).¹⁶

TWI in anterior leads has, in addition, been associated with a worse outcome. Kucher et al. found that TWI in lead V_2 was a predictor of escalation of therapy (40% vs 17%, $P = 0.0009$),⁵³ but did not find a relationship with in-hospital mortality. Another small study reported that TWI in leads V_1 - V_3 was associated with a poor prognosis in 80% of patients and that 86% of patients with this ECG finding went on to require surgical embolectomy.³¹ TWI in leads V_2 or V_1 - V_4 is also associated with a pulmonary vascular obstruction index of $>50\%$ (72% vs 28%, $P = 0.42$; 82% vs 18%, $P = 0.32$, respectively).⁴² Meanwhile, anterior TWI was found to be more likely in patients with massive PE compared with nonmassive PE (85% vs 19%), with a PPV of 93% for severe PE.³⁷ Furthermore, Kukla et al. found

that patients with acute PE and TWI in leads V_2 - V_4 were more likely to develop cardiogenic shock (52% vs 38%, OR 1.18, $P = 0.011$),¹⁸ but was not predictive of survival from shock. In a prior study, this group had also demonstrated an association between TWI in leads V_2 - V_4 and mortality from acute PE (58% mortality vs 39% survival, $P = 0.04$),²⁶ but this finding was not reproducible.¹⁶ However, they did demonstrate that TWI in leads V_2 - V_4 was associated with a complicated hospital course (58% vs 35%, $P = 0.0005$).¹⁶ Finally, while Toosi et al. found that TWI in leads V_1 - V_4 was associated with abnormal RV contraction, they found that only TWI in lead V_1 significantly correlated with complicated in-hospital course (45% vs 22%, $P < 0.05$), while TWI in other anterior leads had a nonsignificant trend toward increased complications in-hospital and TWI in leads V_1 - V_4 were nonsignificantly associated with in-hospital death.⁴¹

In fact, while Kukla found an association between anterior TWI and mortality,²⁶ several studies have not reproduced this finding. Geibel et al. found no significant difference between TWI in leads V_2 and V_3 or V_4 - V_6 in survivors versus nonsurvivors (50% vs 44%, $P = \text{NS}$; 34% vs 42%, $P = \text{NS}$, respectively).¹⁴ Agarwal et al. reported that TWI pattern in right precordial leads was the most prevalent pattern in acute PE, but that it was not found to be a useful predictor of adverse prognosis as this ECG abnormality was found in 64% of survivors, 15% of nonsurvivors and 24% of patients with a poor clinical condition.²³ Furthermore, no significant difference was found in in-hospital mortality with the presence of TWI in more than two anterior ECG leads in patients with massive PE (32% mortality TWI+ vs 35% TWI-, $P = \text{NS}$) or submassive PE (4.5% TWI+ vs 5.3% TWI-, $P = \text{NS}$).⁵⁹ Similarly, using the 21-point ECG score by Daniel's group, Kostrubiec et al. were not able to find a significant association between TWI in any of leads V_1 , V_2 , or V_3 with in-hospital complications or death, though there was a nonsignificant trend toward higher mortality if TWI was present.³⁸ Kumasaka et al. did not find TWI in leads V_1 - V_3 to be a predictor of in-hospital mortality in either acute or chronic PE.⁴⁵ Finally, neither TWI in leads V_2 - V_4 , nor abnormal repolarization in leads V_1 - V_3 , were found to be predictive of hemodynamic instability from acute PE.^{20,54}

T-Wave Inversion in Other Leads and Depth of T Wave. In terms of overall presence of TWI, Kosuge et al. published convincing evidence of the prognostic value of inverted T waves in any lead in patients with acute PE.²⁴ They classified patients into one of three groups according to the number of ECG leads with inverted T waves on admission (low risk ≤ 3 leads, moderate risk 4–6 leads, high risk ≥ 7 leads) and found that RVD correlated with number of T waves involved (47%, 92%, and 100%, respectively, $P < 0.01$), as did in-hospital complications (0%, 8%, and 46%, respectively, $P = 0.004$). On multivariate analysis, they found that inverted T waves in ≥ 7 leads at the time of admission had an OR of 16.8 for in-hospital complications ($P = 0.037$).²⁴ Of note, all of leads V_2 – V_5 were significantly correlated with assigned severity classification. Furthermore, Kukla et al. found that patients with acute PE and a positive troponin had TWI in more ECG leads than those with a normal troponin (3.84 vs 2.1 leads, $P = 0.0001$).¹⁶ and that the number of ECG leads with TWI was an independent predictor of in-hospital complications (3.9 vs 2.7 leads, $P = 0.003$; OR 1.46, $P = 0.001$) and death (4.2 vs 2.8 leads, $P = 0.006$; OR 1.68, $P = 0.00068$).²⁶ This group also found that TWI in leads III and aVF had an OR of 2.27 ($P = 0.06$) for in-hospital mortality, as did the total number of leads with TWI (OR 1.16, $P = 0.054$).¹⁶ More recently, they demonstrated that TWI in five or more leads predicted in-hospital complications (OR 2.07, $P = 0.004$) and mortality (OR 2.92, $P = 0.002$).⁵²

It seems as though the number of involved leads may be more prognostically important than TWI in inferior leads as Zhan et al. found no association between TWI in leads II, II, and aVF with hemodynamic instability²⁰ and Kukla et al. found no significant association between TWI in II, II, and aVF or V_2 – V_4 with mortality, in-hospital complications or cardiac biomarkers.¹⁷ Similarly, Yoshinaga et al. found no significant difference between high-risk and low-risk PE patients for TWI presence in one or more leads,²² and it may be that the total number of leads with TWI is prognostically more important.

The 21-point ECG score by Daniel et al. assigns additional points for depth of TWI. Since then, only Kukla et al. have assessed the significance of this ECG finding (Fig. 1B). They found that the sum of the amplitude of negative T waves was an independent predictor of in-hospital complications

(6.3 mm vs 4.9 mm, $P = 0.04$, OR 0.88, $P = 0.022$) and death (5.9 mm vs 5.1 mm, $P = \text{NS}$; OR 0.81, $P = 0.0098$),²⁶ and later went on to demonstrate that a sum of amplitude of TWI ≥ 5 mm was predictive of in-hospital complications (OR 2.06, $P = 0.002$) and mortality (OR 2.17, $P = 0.023$).⁵² Furthermore, patients with the sum of amplitude of TWI ≥ 5 mm had higher rate of fibrinolytic therapy (14.1% vs 4.0%, OR 3.9, $P < 0.001$), vasopressor support (17.5% vs 7.6%, OR 2.57, $P = 0.002$) and elevated cardiac biomarkers (67.1% vs 45.5%, OR 2.44, $P < 0.001$) than their counterparts with a sum of amplitude of TWI < 5 mm.⁵²

Perhaps TWI in anterior leads does not tell the whole story. It seems as though anterior TWI is prognostically associated with RVD, elevated troponin and perhaps in-hospital complications, but that the total number of ECG leads with TWI may be more prognostically significant. Given the limited number of studies assessing depth of TWI, the prognostic value of ECG abnormality is uncertain. For this reason, the 21-point ECG score by Daniel et al. may require revision.

S1Q3T3 and S1Q3

One of the most historically classic ECG findings associated with PE is the S1Q3T3 pattern (Fig. 2), first described by McGinn and White in 1935.⁶⁰ They presented seven patients with acute cor pulmonale secondary to PE in which they observed a prominent S wave in lead I, a gradual staircase ascent of the ST segment in lead II and a Q wave, and TWI in lead III. However, this finding has since been deemed to be relatively insensitive for PE.¹⁹ Several studies have described the prevalence of the S1Q3T3 sign in PE, with variable rates from 11% to 52%.^{10,37,47,49,51,61,62} In some cases, no significant difference was found in the presence of S1Q3T3 between patients with PE and patients without PE,^{10,51} though the sign was reported to differentiate between patients with acute coronary syndromes (ACS) and PE.¹²

However, it was recognized in 1977 that the S1Q3T3 pattern was found more frequently in patients with severe PE presenting as syncope, with 47% of patients with syncope demonstrating the pattern compared to 8% of patients without syncope ($P < 0.001$).⁵⁵ This may be due to the fact that the S1Q3T3 sign has been associated with RV strain and is reported to occur more commonly

Figure 2. ECG of patient with acute pulmonary embolism after onset of hemodynamic instability demonstrating several abnormalities (reproduced from Zhan et al²⁰ with permission © 2014 Wiley Periodicals, Inc.). STD=ST depression, STE=ST elevation.

in patients with PE and RVD compared to those without RVD (24% RVD+ vs 4% RVD-, $P < 0.001$; 20% RVD+ vs 2% RVD-, $P < 0.001$; 40% RVD+ vs 3% RVD-, $P < 0.001$).^{21,41,44} Since then, S1Q3T3 has been shown to be a predictor of in-hospital complication (37.5% vs 16.7%, $P = 0.004$,³⁸ 35% vs 6%, $P < 0.001$;⁴¹ OR 2.43, $P = 0.049$;¹⁷ OR of 2.17, $P = 0.009$;²³ OR 3.13, $P < 0.001$ ⁵²); is

associated with cardiogenic shock (OR 2.85, $P < 0.001$),¹⁸ is significantly more common in patients with elevated cardiac biomarkers (43% vs 21%, $P = 0.003$),¹⁶ and is a predictor of mortality (58% dead vs 28% alive, $P = 0.006$;²⁶ 27% dead vs 9% alive, $P < 0.001$;⁴¹ OR 5.61, $P = 0.005$;¹⁷ OR 3.52, $P < 0.001$ ⁵²). A Japanese case series of 16 patients even found S1Q3T3 to be the most frequently observed abnormality in the setting of acute massive PE.²² Of note, one study reported S1Q3T3 to occur in only 18% of patients with massive PE, but, in this older study, massive PE was defined by degree of obstruction or filling defect,³⁶ and as such is not representative of the current definition of massive PE characterized by hypotension or cardiogenic shock.

Several studies have also found statistically nonsignificant trends toward association of the S1Q3T3 sign with adverse prognosis, including higher association with elevated cardiac biomarkers (31% Trop+ vs 13% Trop-, $P = \text{NS}$),⁴⁷ and a trend toward association with patients at high risk of death or complicated hospital course (45% high risk, 18% medium risk, 14% low risk, $P = \text{NS}$).²⁴ Furthermore, the frequency of S1Q3T3 increases with mean pulmonary artery pressure (MPAP), with 57% of patients with MPAP ≥ 40 mmHg exhibiting the pattern, compared to only 43% with MPAP ≤ 40 mmHg.²² Another study found that S1Q3T3 had an OR of 2.21 for predicting in-hospital death in acute PE, but the confidence interval crossed 1,⁴⁵ while others have found no significant difference in mortality between patients with S1Q3T3 and those without, though these studies were limited by smaller sample sizes.^{25,38}

Interestingly, Zhan et al.²⁰ reported that, at baseline diagnosis of PE, S1Q3T3 occurred in 25% of patients and S1Q3 pattern occurred in 30% of patients, but upon hemodynamic deterioration, the S1Q3 sign was found to significantly increase in frequency (75%, $P = 0.004$), but not the S1Q3T3 sign (45%, $P = \text{NS}$). Gallota et al. also reported the S1Q3 sign in 15% of patients developing hemodynamic stability compared to 2% without ($P = 0.04$).⁵⁴ When the S1Q3T3 pattern has been analyzed according to its individual components, a Q wave in lead III was found in 71% of patients, and an S wave in lead I was found in 69% of patients, with acute massive or submassive PE.³¹ Another study of acute PE reported an S wave in lead I and aVL in 73% of patients, Q wave in

lead III and aVF in 49% of patients, and TWI in lead III and aVF in 33% of patients.¹¹ In terms of prognostication, Toosi et al. found that a S wave in lead I and a Q wave in lead III were associated with abnormal RV contraction (58% vs 23%, $P < 0.001$ and 55% vs 25%, $P < 0.05$, respectively).⁴¹ Notably, TWI was more frequently found in patients with longer clinical histories, many of which had symptoms for greater than 7 days.¹¹ Given these findings, the S1Q3 may be a more sensitive ECG finding for PE with hemodynamic instability and may be useful in risk stratification for PE.²⁰

Evidence suggests that the S1Q3T3 finding may also be more common in the acute phase of PE as suggested by a transient S1Q3T3 pattern detected during the acute phase of RVD¹⁵ and the tendency for S1Q3T3 to disappear during the chronic phase of PE.²²

Overall, while the S1Q3T3 pattern may be insensitive for diagnosing all PEs, it is a very specific finding (97%) for all PE,¹⁹ and its prognostic value is significant for predicting which patients are likely to have RV strain or other adverse events. It is also more likely to be present during the acute phase of PE. Meanwhile, the S1Q3 finding may be even more useful in risk stratification for PE given its more common occurrence in hemodynamically unstable PE.

ECG Abnormalities Not Included in 21-Point ECG Score

ST-Segment Depression

Though ST-segment depression (STD) is not an ECG abnormality that is included in Daniel's 21-point ECG score, several studies have described potential prognostic value associated with this sign (Fig. 2). Kukla et al. found that STD in leads V₄–V₆ was present in over 26% of all patients with acute PE, of which 24% survived and 46% died ($P = 0.03$), and 22% had a noncomplicated stay while 40% suffered in-hospital complications ($P = 0.003$).²⁶ They had previously reported that STD in these leads had an OR of 2.31 ($P = 0.05$) for in-hospital mortality.¹⁶ Another group found that STD in leads I, II, and V₄–V₆ was present in 38% of survivors of acute PE compared with 49% of nonsurvivors ($P = 0.03$), with a negative predictive value of 81% for 30-day mortality.¹⁴ Furthermore, in the setting of acute PE, STD in leads V₄–V₆ has been associated with cardiogenic shock (52%

vs 25%, OR 4.35, $P < 0.001$),¹⁸ positive troponin (40% vs 14%, $P = 0.0001$),¹⁶ and hemodynamic deterioration.²⁰ In fact, Zhan et al. reported STD to be present in leads V₄–V₆ in 10% of patients at baseline diagnosis of PE and in 90% of patients who went on to deteriorate hemodynamically ($P = 0.001$). They noted a similar finding with STD in leads V₅ and V₆ with no patient exhibiting this finding at baseline, but upon hemodynamic deterioration, it was observed in 90% of patients ($P = 0.001$).²⁰ Of note, they also reported a similar finding for STD in lead I, with only 5% of patients exhibiting this finding at baseline diagnosis of PE and 100% of patients with this abnormality upon hemodynamic deterioration. Finally, it appears as though the finding of STD is more likely to occur in the setting of acute PE rather than chronic PE.⁴⁵

Other studies have not found such a strong association between STD and prognostic outcome from PE, though most of these studies are nondiscriminatory regarding the lead in which STD is observed, which may limit their usefulness. Janata et al. found no significant difference in-hospital mortality in patients with massive or submassive PE.⁵⁹ Several other studies have found no significant difference in the prevalence of STD in different risk categories of PE based on clinical outcomes or number of leads with TWI,^{22,24,36} nor was there an association between STD and RV enlargement.¹⁹

ST Elevation (STE)

Several patterns of STE have been described in terms of prognostic association with acute PE (Fig. 2). Some investigators have assessed for the role of STE in any lead in terms of predicting outcome in acute PE. STE of 1 mm or more in any lead except aVR has been reported in 16–48% of patients but has not been found to accurately prognosticate according to severity of PE on its own.^{22,24,36} STE in any lead also did not prognosticate for RV enlargement.¹⁹ Meanwhile, STE in lead V₂ was found to be associated with hemodynamic deterioration due to PE (5% of patients at baseline vs 45% after hemodynamic instability, $P = 0.003$), but the same was not found for STE in lead V₃.²⁰ Furthermore, STE in leads I, II, and V₄–V₆ was found to be more prevalent in nonsurvivors compared with survivors (16% vs 6%, $P = 0.001$) with a specificity of 94% for 30-day mortality.¹⁴ The most direct evidence supporting a

possible prognostic role in acute PE can be found for STE in leads III, V₁ and aVR as described below.

STE in Lead III. STE in lead III has more recently gained attention as a possible prognostic marker in acute PE (Fig. 2). It has been reported to be present in only about 13% of patients with acute PE, but was present in 30% of patients who died and only 11% of patients who survived ($P = 0.03$),²⁶ with an OR of 2.64 for in-hospital mortality ($P = 0.048$).⁶³ STE in lead III has also been associated with a complicated hospital stay (23% vs 10%, $P = 0.000$),²⁶ cardiogenic shock (29% vs 9%, OR 2.46, $P = 0.004$),¹⁸ hemodynamic instability (0% at baseline vs 65% after hemodynamic instability, $P = 0.001$)²⁰ and elevated troponin (22% Trop+ vs 7% Trop-, $P = 0.0006$).¹⁶

STE in Lead V₁. The finding of STE in lead V₁ has also gained recent attention for its prognostic role in the setting of acute PE (Fig. 2). It has been reported to be present in 25–34% of patients with acute PE.^{18,26} It is an independent prognostic ECG parameter of in-hospital death (61% of deceased patients, 20% of alive patients, $P = 0.0001$; OR 4.47, $P = 0.0003$) as well as in-hospital complications (52% of patients with complications vs 16% without, $P = 0.000$; OR 3.99, $P = 0.00017$).²⁶ It has also been found to be associated with cardiogenic shock (57% vs 16%, OR 6.78, $P < 0.001$), but was not predictive of survival from cardiogenic shock.¹⁸ Others have reported association with hemodynamic instability (5% at baseline vs 85% with deterioration, $P = 0.001$),²⁰ positive troponin (43% vs 10%, $P = 0.0001$; 40% vs 10%, $P = 0.002$),^{16,53} RVD (12% vs 3%, $P < 0.05$),⁵³ and escalation of therapy (40% vs 13%, $P = 0.02$), though this latter study did not find STE in lead V₁ to be predictive of in-hospital death.⁵³ Only one study that has assessed the prognostic role of STE in lead V₁ has not found a significant association with this ECG abnormality and mortality in patients with massive and submassive PE, though there was a trend towards a higher mortality in patients with this ECG finding and massive PE (41% dead vs 27% alive).⁵⁹

STE in Lead aVR. Finally, the finding of STE in lead aVR (Fig. 2) is gaining recognition as a potential prognostic marker despite the fact

that this lead was frequently excluded from ECG analysis in the setting of acute PE in the past.^{22,36} It has been reported to be present in 30–43% of patients with acute PE.^{18,26,59} It has been associated with a higher mortality (67% vs 40%, $P = 0.004$),²⁶ in-hospital complications (70% vs 36%, $P = 0.000$; OR 2.49, $P = 0.002$),²⁶ hemodynamic deterioration (baseline 5% to 95% with hemodynamic instability, $P = 0.001$),²⁰ and cardiogenic shock (65% vs 30%, OR 4.35, $P < 0.001$).¹⁸

Two studies have closely assessed the prognostic role of STE in lead aVR in the setting of acute PE. Both Janata et al. and Kukla et al. have studied large numbers of patients with acute PE (396 and 293, respectively) and found STE in lead aVR to be present in 34.3% and 45.3% of patients, respectively.^{59,64} Both groups found that patients with this ECG finding were more likely to have positive troponin levels (0.035 vs 0.01, $P < 0.001$; 64.8% vs 27.9% of patients, $P < 0.001$), exhibit hypotension with a systolic BP <90 mmHg (17% vs 6.5%, $P = 0.001$; 27% vs 10%, $P < 0.001$), require thrombolytic therapy (29.1% vs 7.5%, $P < 0.001$; 14.3% vs 5.6%, $P = 0.009$) and have higher in-hospital mortality (10.3% vs 5.4%, $P = 0.07$, 16.5% vs 6.9%, $P = 0.009$).^{59,64} Janata et al., in addition, demonstrated that patients with acute PE and STE in lead aVR had echocardiographic evidence of RVD (74.5% vs 47%, $P < 0.001$), central PE on CTPA (51% vs 29%, $P < 0.001$), and were more likely to have evidence of tachypnea (31% vs 12%, $P < 0.001$), dyspnea at rest (45% vs 29%, $P = 0.002$), syncope (16% vs 6.5%, $P = 0.002$), and tachycardia (37% vs 23%, $P = 0.003$).⁵⁹ Meanwhile, Kukla et al., in addition, demonstrated that patients with acute PE and STE in lead aVR required more vasopressor support (29.3% vs 7.5%, $P < 0.001$), had higher rates of in-hospital complication (38.3% vs 12.5%, $P < 0.001$), and were more likely to exhibit other ECG abnormalities such as TWI in inferior leads, STE in lead III, STE in lead V₁, ST depression in leads V₄–V₆, RBBB, QR sign in lead V₁ as well as S1Q3T3.⁶⁴ As such, both Janata and Kukla's groups demonstrated that STE in aVR is associated with a more severe clinical course and correlates with several other markers of severity in acute PE. Further studies are required to strengthen the evidence in this regard.

qR/QR/qr in Lead V₁

The potential prognostic value of the presence of qR, QR, or qr in lead V₁ as an ECG finding in

PE is recently gaining attention (Fig. 2). This ECG finding is a marker of RV strain or dysfunction.¹⁶ In 2003, Kucher et al. found the QR sign in lead V₁ in 19% of patients with PE compared to 0 patients without ($P < 0.0001$), corresponding to a sensitivity of only 19% but a specificity of 100% and NPV of 100%.⁵³ They also found that this sign was associated with RVD (31% with vs 3% without, $P < 0.01$) and a positive troponin (36% vs 19%, $P = 0.008$). Kukla et al. similarly found that patients with PE and a positive troponin were more likely to exhibit a qR in V₁ than those patients with a negative troponin (16% vs 5%, $P = 0.007$).¹⁶ In logistic regression analysis, this ECG sign had an OR of 4.45 for predicting in-hospital mortality ($P = 0.0039$). Another study by the same group found that, in patients with PE, the qR or QR morphology in lead VI was much more likely to be present in patients with cardiogenic shock than those without (25% vs 8%, $P < 0.001$), corresponding to an OR of 3.63 for association with cardiogenic shock.¹⁸ QR in lead V₁ has also been associated with need for escalation of therapy (55% vs 6%, $P < 0.0001$),⁵³ in-hospital complications (21% vs 8%, $P = 0.004$),²⁶ and overall mortality (30% nonsurvivors vs 9% survivors, $P = 0.0002$).²⁶ Most recently, Zhan et al. reported new onset Qr sign in 35% of patients that developed hemodynamic instability with PE. Considering that two other patients developed the Qr sign from a notched S wave or from RBBB, a total of 45% of patients with PE who developed hemodynamic instability exhibited the Qr sign.²⁰ This led Zhan et al. to suspect that the Qr sign may be prognostically associated with more severe PE.

Low QRS Voltage

Low QRS voltage in the peripheral leads, defined by the greatest overall deflection in the QRS complex measuring ≤ 5 mm in all limb leads, is a frequently described ECG finding in acute PE, though with quite variable incidence of 3–30%.^{10–12,24,36,37,50,51,65} It has been reported to be much more common in patients with PE than with ACS.¹²

As with other reported ECG findings, low QRS voltage appears to be associated with more severe PE. In fact, though low QRS voltage was reported in only 19% in one case series, 75% of these patients had a MPAP ≥ 40 mmHg.²² Peripheral low voltage was also found to be significantly

higher in nonsurvivors with acute PE compared to survivors (35% vs 22%, $P = 0.005$).¹⁴ Though this correlated with only 35% sensitivity for 30-day mortality, specificity was reasonable at 79% with a negative predictive value of 81%.¹⁴ This ECG finding has also been independently associated with cardiogenic shock with an OR of 3.44 ($P < 0.001$).¹⁸

However, not all studies have found an association with low-voltage QRS and severity of PE. There was no correlation between troponin level and presence of low-voltage QRS,¹⁶ nor was there association found with RVD.¹⁵ Though there has been no significant association of this ECG sign with in-hospital complication or mortality, there has been a nonsignificant trend in this regard with 50% of high-risk PE patients demonstrating low voltage compared 15% of lower risk patients ($P = \text{NS}$).²⁴ Meanwhile, low-voltage QRS has been associated with a nonsignificant increase in mortality (12% vs 7%, $P = \text{NS}$) and in-hospital complications (12% vs 6%, $P = \text{NS}$).²⁶ Another study looking at low QRS voltage in the frontal plane found no significant association with RV enlargement,¹⁹ though did find an overall high specificity of 99% for low-voltage QRS in all PE. Finally, another study assessing the incidence of low-voltage QRS in the frontal plane found a low rate of 6% with no significant difference noted between patients with and without PE.⁵¹ Of interest, low-voltage QRS appears to be more common in patients with chronic PE rather than acute PE, though the finding did not reach statistical significance (15.1% vs 5.2%, $P = 0.07$).⁴⁵

Axis Deviation

Several studies have investigated the potential prognostic role of the ECG finding of axis deviation in the setting of acute PE, with some focusing on right axis deviation (RAD) and others investigation left axis deviation (LAD).

In terms of RAD, Agarwal et al. found that RAD was present in 38.4% of survivors, compared with 72% of nonsurvivors, and 48.7% of patients with a poor clinical condition from PE ($P = 0.002$).²³ In keeping with this, Kumasaka et al. found that the presence of RAD was associated with an OR of 10.5 for in-hospital death ($P = 0.006$).⁴⁵ Ermis et al. also found an association between presence of RAD and severity of PE with this finding in 3% of low-risk PE, 15% of submassive

PE and 28% of massive PE ($P = 0.009$),⁶⁶ while Yoshinaga et al. found an association between RAD and severity of PE as defined by MPAP ≥ 40 mmHg with only patients in this high-risk group exhibiting this finding.²² However, several studies have not found an association between RAD and elevation of cardiac biomarkers,¹⁶ RV enlargement,¹⁹ risk stratification for PE,^{24,36} in-hospital complications,²⁶ or mortality.²⁶

In terms of the finding of LAD on ECG, most studies have found no significant association with elevation of cardiac biomarkers,¹⁶ RV enlargement,¹⁹ severity of PE,^{22,36,66} complicated course,²⁶ or mortality.²⁶ In fact, only one study has found an association between LAD and severity of PE with Kosuge et al. observing an overall presence of LAD in 8% of patients with acute PE, all of which occurred in the highest risk group ($P = 0.024$).²⁴

Meanwhile, Kucher et al. investigated the role of axis deviation in the setting of PE and reported the presence of elevated biomarkers in patients with a clockwise rotation of the QRS vector in precordial leads or a QRS axis $>50^\circ$, but there was no association with the need for escalation of therapy or in-hospital death.⁵³

QRS Fragmentation

QRS fragmentation, or a notched QRS, is gaining recognition for its potential association with PE, particularly in hemodynamically unstable patients. It has been reported in almost 20% of patients with cardiogenic shock and PE compared to 8% in patients with PE and no cardiogenic shock, and was found to be an independent predictor of cardiogenic shock in multivariate regression analysis with an OR of 3.00.¹⁸ Abnormal QRS morphology in V_1 was also shown to be present in 20% of patients with PE at baseline, but increased to 95% prevalence in patients who subsequently developed hemodynamic instability,²⁰ again suggesting that it may correlate with severity of PE. However, it has not been found to be associated with mortality,¹⁸ or with cardiac biomarkers¹⁶ and has not been frequently described except in recent years.

Supraventricular Tachycardia

A few studies have assessed the prognostic role of the ECG finding of tachycardia in the setting of PE, without specifying the presence of sinus

tachycardia or that from other arrhythmias. Kucher et al. found that an ECG finding of a heart rate > 100 bpm was associated with escalation of therapy in 70% of patients with PE versus 27% of patients without tachycardia.⁵³ Tachycardia on ECG has also been associated with higher mortality (40% mortality vs 23% survival, RR multivariate analysis 2.4, $P = 0.003$; OR 4.21, $P = 0.026$).^{16,25} However, others have found that tachycardia on ECG did not prognosticate between risk categories of PE,⁶⁶ for in-hospital mortality⁵³ or for positivity of cardiac biomarkers.⁵³

Meanwhile, in a recent large study of 975 patients by Kukla et al., atrial fibrillation was found in 231 (24%) of patients with acute PE, and its presence was associated with a higher risk of mortality (23% vs 12%, OR 2.1, $P < 0.001$) and complications (31% vs 20%, OR 1.8, $P < 0.001$).⁶⁷ A significantly smaller study also found atrial fibrillation to be associated with a higher risk of complicated hospital course (32% vs 18%, $P = 0.01$), but this was not significant in multivariate analysis.²⁶ In other small studies, atrial fibrillation was associated with higher mortality with borderline statistical significance (29% vs 10%, multivariate analysis RR 2.8, $P = 0.05$),²⁵ but was not found to be significant associated with mortality in others (33% vs 20%, $P = 0.07$, OR = NS),^{16,26} nor was there an association with cardiogenic shock (OR 1.63, $P =$ NS).¹⁸ Finally, the presence of atrial fibrillation did not appear to predict positivity of cardiac biomarkers^{16,47} or presence of RV enlargement.¹⁹

P Pulmonale

P pulmonale refers to a peaked P wave on ECG with amplitude greater than 2.5 mm in the inferior leads or greater than 1.5 mm in V_1 and V_2 that is produced by right atrial enlargement, principally caused by pulmonary hypertension.^{17,22} P pulmonale has been reported to occur in 0–19% of patients with acute PE.^{15,22,24,36} A few studies have assessed the prognostic value of P pulmonale in the setting of acute PE, but none have found a significant association between P pulmonale and outcome from acute PE, including no significant difference in severity of PE,^{24,36} in-hospital complications,²⁶ or mortality.²⁶ There has also been no association found with RV enlargement¹⁹ or elevation in cardiac biomarkers.¹⁶ One study found that of the four patients with acute

PE and P pulmonale (19% of all patients with acute PE), three had a MPAP ≥ 40 mmHg, but this study is limited by small sample size.²² Overall, there does not seem to be much prognostic value for P pulmonale in the setting of acute PE.

Long QT

Evidence is accumulating for the potential prognostic value of a long QT interval in acute PE. Though the majority of evidence only exists in the form of case reports,⁶⁸⁻⁷⁰ Punukollu et al. describe a series of five acute PE patients with QT interval prolongation and global TWI (3.5% of studied patients with PE), all of which had changed characteristic of hemodynamically significant PE, including RV stunning or hypokinesis and dilatation or paradoxical septal motion.⁷¹ One patient is reported to have died, and in the remainder, ECG abnormalities gradually resolved over a week. Since then, Buppajarntham et al. performed a retrospective chart review of 300 patients diagnosed with PE and found that the patients with a prolonged QTc (>460 ms) demonstrated significantly increased RV dilatation (OR 1.8) and systolic dysfunction (OR 3.1). Additionally, in the prolonged QTc group, the duration of hospitalization and intensive care unit stay was longer (OR 4.1 and OR 2.3, respectively) and they had more hypotensive episodes and received thrombolytic treatment more frequently (OR 4.3 and OR 7.7, respectively). There was no statistical difference in in-patient mortality rates. Further investigation is required to more clearly delineate the potential role for long QT as a prognostic marker in acute PE.

QT Dispersion

QT dispersion (QTcd) has also gaining attention in terms of a potential prognostic marker in PE. Ermis et al. stratified patients into categories of risk based on the 21-point ECG score by Daniel et al. and found that the QTcd was higher in the high-risk group (95.9 ± 33.2) than in low and intermediate risk groups (59.5 ± 23.4 , $P < 0.001$ and 69.2 ± 21 , $P = 0.01$, respectively).⁶⁶ They also found that patients who died as a result of acute PE had significantly higher QTcd values at baseline compared with the QTcd values of surviving patients (89.1 ± 45.5 vs 65 ± 22.9 , $P = 0.001$), and the sensitivity and specificity for prediction of mortality was 71% and 73%, respectively ($P = 0.001$). They also found a strong

correlation between QTcd and ECG score values ($r = 0.69$, $P < 0.001$) as well as pulmonary artery pressures ($r = 0.27$, $P = 0.05$).

Brugada

Though no studies describing the Brugada phenocopy (Fig. 3) in acute PE have met our predefined requirements of an observational study or case series with a predefined endpoint, case reports and small case series are emerging that report an association in this regard.^{72,73} Further characterization of the potential role of the Brugada phenocopy in acute PE is required to determine if there is a prognostic association.

Combinations of Findings

Some studies have investigated the prognostic role of combination of findings, particularly in terms of nonspecific ST-segment or T-wave abnormalities, with some success in prognosticating for PE. Kukla et al. found an association between "the presence of at least 1 lead with STE out of leads III, aVR, and V_1 - V_4 or STD in at least 2 lateral leads" and mortality (OR 6.35, $P = 0.007$), but did not find an association with a "global ischemic pattern" or "negative T wave pattern."¹⁷ Stein et al. found an association between "nonspecific T-wave changes" and RV enlargement (33% vs 24%, $P = 0.002$), as well as an association between "ST-segment or T-wave changes" and RV enlargement (52% vs 28%, $P < 0.0001$).¹⁹ Finally, Zhan et al. found that several combinations of findings predicted development of hemodynamic instability including: "STE in lead aVR with concomitant STD in leads I and V_4 - V_6 ," "STE in leads V_1 - V_3 / V_4 ," "STE in leads III and/or V_1 / V_2 with concomitant STD in leads V_4 / V_5 and V_6 ," and "STE and STD with concomitant S1Q3 and/or abnormal QRS morphology in lead V_1 " (all significant with $P \leq 0.001$).²⁰ Meanwhile, Escobar et al. did not find any association with "ST-segment or T-wave abnormalities with survival,"²⁵ nor does there appear to be a significant association between "ST-segment depression and TWI in V_1 - V_4 " and presence of trunk embolism versus peripheral embolism,⁴⁶ or with "ST-T alterations" and elevation of troponin.⁴⁷

Given that studies have investigated different combinations of findings, it is difficult to draw any specific conclusions regarding the utility of these combinations in the prognostication of PE as they require further evaluation.

Figure 3. ECG from patient with acute pulmonary embolism depicting a type-1 Brugada pattern (reproduced from Zhan et al⁷³).

CONCLUSION

Acute PE remains a frequent cause of cardiovascular morbidity and mortality. Mounting evidence suggests that ECG can play a valuable role in prognostication for PE, particularly when modern technology may not be readily accessible. The historical 21-point ECG prognostic score by Daniel et al. was a valiant attempt to provide a usable clinical ECG tool as a prognostic instrument. However, recent evidence suggests that several ECG abnormalities that have the ability to provide valuable prognostic information are not included in this tool. These include: TWI in leads other than precordial leads, STD, STE, the QR sign, QRS fragmentation, atrial fibrillation. Other ECG abnormalities requiring more evidence to support their potential prognostic role include: low-voltage QRS, axis deviation, P pulmonale, LQT, QT dispersion, and Brugada pattern. Meanwhile, the value of the ECG to identify patients with a low prognostic risk has yet to be determined. This highlights the need for a meta-analysis regarding the prognostic role of the above ECG abnormalities and perhaps a revised scoring system that could assist with predicting outcome and severity of PE.

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