Findings from 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: systematic review and meta-analysis

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Jacob D. Shopp MD
Lauren K. Stewart MD

Thomas W. Emmett, MD, MLS
Clinical Informationist
Ruth Lilly Medical Library
Indiana University School of Medicine
Indianapolis, IN 46202

Jeffrey A. Kline, MD
Vice Chair of Research
Department of Emergency Medicine
Professor, Department of Cellular and Integrative Physiology
Indiana University School of Medicine
720 Eskanazi Avenue
Indianapolis, IN 46202
jefkline@iu.edu

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Abstract

Background: Treatment guidelines for acute pulmonary embolism (PE) recommend risk-stratifying patients to assess PE severity, as those at higher risk should be considered for therapy in addition to standard anticoagulation to prevent right ventricular (RV) failure, which can cause hemodynamic collapse. We hypothesize that 12-lead electrocardiography (ECG) can aid in this determination. The objective of this study was to measure the prognostic value of specific ECG findings (the Daniel score, which includes heart rate over 100 beats/min, presences of the S1Q3T3 pattern, incomplete and complete right bundle branch block (RBBB), and T wave inversion in leads V1-V4) plus ST elevation in AVR and atrial fibrillation suggestive of RV strain from acute pulmonary hypertension in patients with acute PE.

Methods: Studies were identified by a structured search of MEDLINE, PubMed, EMBASE, the Cochrane library, Google Scholar, Scopus and bibliographies in October 2014. We excluded case reports, non-English papers and those that lacked either patient outcomes or ECG findings. We included papers with evidence of a predefined reference standard for PE and the results of 12-lead ECG, stratified by outcome (hemodynamic collapse, defined as circulatory shock requiring vasopressors or mechanical ventilation, or in-hospital or death within 30 days). Papers were assessed for selection and publication bias. We also assessed heterogeneity (I^2) and calculated the odds ratios for each ECG sign from the random effects model if I^2>24% and fixed effects if I^2<25%. Funnel plots were used to examine for publication bias.

Findings: Forty-five full-length studies of 8,209 patients were analysed. The most frequent ECG signs found in patients with acute PE were tachycardia (38%), T wave inversion in lead V1 (38%) and ST elevation in aVR (36%). Ten studies with 3,007 patients were included for full analysis. Six ECG findings (heart rate >100, S1Q3T3, complete RBBB, inverted T waves in V1-V4, ST elevation in aVR and atrial fibrillation) had likelihood and odds ratios with lower limit 95% confidence intervals above unity, suggesting them to be significant predictors of hemodynamic collapse and 30-day mortality. Odds ratio

data showed no evidence of publication bias, but the proportions of patients with hemodynamic collapse or death and S1Q3T3 and RBBB tended to be higher in smaller studies. Patients who were outcome negative had a significantly lower mean Daniel score (2.6±1.5) than patients with hemodynamic collapse (5.9±3.9 vs. P=0.039, ANOVA with Dunnett's post-hoc), but not patients with all-cause 30 day mortality (4.9±3.3, P=0.12).

Interpretation: Systematic review and meta-analysis revealed 10 studies including 3,007 patients with acute PE, six findings of RV strain on 12-lead ECG (heart rate >100, S1Q3T3, complete right bundle branch block, inverted T waves in V1-V4, ST elevation in aVR and atrial fibrillation) significantly increase the risk of circulatory shock and death.

Introduction

Treatment guidelines recommend that clinicians employ a clinical strategy that includes the risk-stratification of patients with PE to estimate the probability of circulatory shock and 30-day all-cause mortality.[1, 2] Experts generally agree that patients with PE and RV failure have an elevated risk of hemodynamic collapse, and should be considered for additional treatment beyond standard anticoagulation including fibrinolytic therapy. [1-3] Patients with low risk PE might be considered for immediate treatment at home.[4-6] Well-recognized methods for risk-stratification include scoring systems, blood biomarkers (troponins I and T, brain natriuretic peptides), echocardiographic findings of right ventricular strain and findings of a dilated right ventricle on CT scanning.[3, 7, 8] The 12-lead electrocardiogram (ECG) also provides information about severity of PE. A scoring system was developed by Daniel et al in 2001 that assigned points (0-21) to ECG components that predicted increased pulmonary arterial pressure (Figure 1).[9] The Daniel score was then found to correspond to the degree of perfusion defect on ventilation-perfusion lung scanning, and a score >8 predicted worsened clinical outcomes, including death, shock or respiratory failure.[10] However, the weights given to the Daniel score components were derived implicitly, and many clinicians believe that other findings, such as ST elevation in aVR and atrial arrhythmias, predict worse outcome from PE.

The purpose of this study was to measure the prognostic value of ECG findings indicative of right ventricular strain from acute pulmonary hypertension in patients with acute pulmonary embolism. To accomplish this, we conducted a systematic literature review and meta-analysis to quantify the value of each component of the Daniel score plus ST elevation in aVR and atrial fibrillation, for the prediction of hemodynamic collapse or death within 30-days in acute PE.

Methods

This study was registered at http://www.crd.york.ac.uk/PROSPERO/ on December 16, 2014 (CRD42014015502). Methods for paper selection and reporting follow the guidelines set forth by the PRISMA statement and those recommended by the MOOSE standardized reporting guidelines.[11, 12]

Population

This study included a population of patients with acute pulmonary embolism, proven by diagnostic testing, with available 12-lead electrocardiography. Patients presented in multiple settings and were not limited to those diagnosed in the emergency department. Full inclusion and exclusion criteria are described in further detail below.

Outcomes

The main question of this work was to determine the quantitative value of each component in Figure 1 (heart rate over 100 beats/min, presences of the S1Q3T3 pattern, unspecified RBBB, incomplete and complete RBBB, and T wave inversion in leads V1-V4), plus ST elevation in aVR and atrial fibrillation for the prediction of either death within 30 days of diagnosis or the development of hemodynamic collapse (defined below). This 30 day outcome includes papers that only reported in-hospital mortality, which usually occurs in the first week after diagnosis. Findings of T-wave inversions in leads V1-V4 were simplified to a binary input (either present or absent) and right bundle branch block (RBBB) was classified as incomplete, complete, or unspecified (either incomplete or complete or not stated). The primary unit of measurement the prevalence of each finding in patients with and without the outcome, because these proportions form the basis of the likelihood and odds ratios.

Literature search

In October 2014, we performed a systematic search of MEDLINE, PubMed (for non-MEDLINE records), EMBASE, the Cochrane library, Google Scholar and Scopus for studies that examined the value of electrocardiographic findings for predicting outcome in patients with pulmonary embolism. We also searched the proceedings of the annual scientific meetings of the American College of Cardiology, American College of Chest Physicians, and the American College of Emergency Physicians for the past 3 years A supplemental PubMed search was performed in April, 2015. Databases were searched from inception, and no additional year limits were applied. Search strategies combined database-specific subject headings and keyword variants for three main concepts – pulmonary embolism, electrocardiography, and prognosis/predictive value. For the electrocardiography concept, specific abnormalities usually diagnosed by ECG were also included in the searches (e.g., bundle branch block, arrhythmias, PR, QRS, QT intervals). Results were limited to the English language, and single case reports were excluded. Detailed search strategies are provided in the on-line supplement #1. A master's level medical librarian (TWE) conducted the database searches. We also searched the bibliographies of meta-analyses and book chapters on topics relevant to PE diagnosis and prognosis: clinical prediction rules[7, 13, 14], clinical pathways and guidelines[1, 3, 15-18] and other diagnostic methods[19-21].

Selection process

Two authors reviewed the results of the search for relevance and independently read the titles and abstracts of all retrieved citations. The same two authors then independently read the retained full-length articles that passed the initial relevance screen for inclusion in the final analysis. We assessed inter-observer reliability with Cohen's kappa. Discordances were resolved by consensus with a third author as arbiter.

Inclusion and exclusion criteria

The initial inclusion criteria were: studies of symptomatic patients who underwent objective diagnostic testing proving PE which included data on risk factors for VTE. Diagnosis of PE required pulmonary vascular imaging demonstrating a filling defect on a contrast enhanced study or unmatched perfusion defects on scintillation lung scan, or autopsy. Retained full-length articles were then read for the following criteria: evidence of a prospective or retrospective selection algorithm with a predefined reference standard for PE that included at least either pulmonary vascular imaging or mixed-objective testing plus clinical outcomes assessed until at least hospital discharge and the results of 12-lead electrocardiography, stratified by outcome. The minimal ECG criteria required to include a study was presence of heart rate, S1Q3T3 and right bundle branch block data. Exclusion criteria included the written statement that hemodynamically unstable patients were excluded, studies without adequate ECG criteria, and those studies that clearly indicated the data were non-additive (i.e., redundant with previously published data), including secondary analyses of other published data. Hemodynamic collapse is defined as systolic blood pressure <90 mm Hg requiring or associated with the use of vasopressors, need for endotracheal intubation, catheter or surgical thrombectomy, any use of thrombolytics, cardiopulmonary resuscitation, extracorporal perfusion. Hemodynamic collapse was assessed up until day of discharge but not beyond; death was reported as all-cause and up to 30 days post PE diagnosis. Patients alive at 30 days without hemodynamic collapse were deemed “outcome negative.” The primary data for analysis are the total number of patients with PE and the number with each outcome. When necessary, we emailed the corresponding authors for additional data up to three times.

Quality Assessment

We graded study quality using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2), using a standard form.[22] Each study was graded as "low risk," "high risk," or "unclear risk" for bias in terms of selection of patients and reference standard. For patient selection, we considered a study low risk if it enrolled patients under conditions similar to what a physician is likely to experience in evaluating a patient with diagnosed PE in the absence of other influences. We considered patient selection bias at high risk if the paper or personal communication with the author indicated that patients were pre-selected or excluded for either more or less severity in terms of presentation (e.g., positive biomarker such as troponin or echocardiography). We considered the reference standard at low risk of bias if all patients included had positive pulmonary vascular imaging and had outcomes followed until hospital discharge. Studies without these criteria had a high-risk reference standard. Studies lacking sufficient criteria to understand patient selection or reference standard had an unclear risk.

Statistical analysis

We generated a table that included total number of PE+ patients, the number of PE+ patients that had each outcome and the pooled true positive and false positive rates for each ECG finding. We assessed for heterogeneity between studies using the inconsistency indexes (I^2 and I^2_v) where I^2 represents the percentage of the total variability in a set of effect sizes due to true heterogeneity, owing to between-studies variability; I^2_v includes a random effects correction term to account for variability in different populations sampled.[23] We calculated the likelihood ratios (LRs) and their 95% confidence intervals (CIs) directly from the pooled true positive and false positive proportions. We calculated the odds ratios for each variable from the random effects model, and the fixed effects OR only if heterogeneity was low (I^2<25%).[24] Unless otherwise stated, all CIs are from the random effects model, otherwise were calculated from the Clopper-Wilson exact binomial formula. The authors prepared a

database in Excel (Microsoft Inc, Redmond, WA) detailing the calculations for the pooled true positive and false positive rates, and the random effects calculations using the method of Neyeloff et al; a copy of the spreadsheet is available from the corresponding author.[23] A funnel plot was used to examine for publication bias using Egger's test of asymmetry with $P>0.1$ considered absence of publication bias.[25] We also performed a post-hoc sensitivity analysis to exclude one study with risk of bias. We calculated the mean Daniel score for patients based upon outcome (negative, hemodynamic collapse, or all-cause death) and compared means (after normality testing with the Shapiro-Wilk test) with one-way analysis of variance with Dunnett's post-hoc test to compare patients with death or hemodynamic collapse to patients who were outcome negative as controls with $P<0.05$ considered significant (StatsDirect, v4.0, Cheshire, England).

Results

Article Selection

The search revealed 3680 unique titles and abstracts that were screened for relevance by two independent reviewers, with 45 selected for full-length review yielding a good combined interobserver reliability for retained studies (κ=0.94; 95% CI 0.89, 1.0). Figure 2 shows the selection process and Table 1 shows the characteristics of each study retained for full-length review, including elements of QUADAS 2. Additionally, on-line supplement #2 shows which ECG components were reported for each of the 45 papers reviewed in full-length, including the prevalence of each component. To provide context about what type of ECG data authors included, Table 2 shows the numbers of patients with each ECG finding that were reported and the percentage of PE patients who manifested the ECG finding of all studies included in Table 1. The ECG features that were most frequently found in patients with PE were tachycardia (HR>100) and T wave inversion in lead V1 (38% each) and ST elevation in aVR (36%). The overall 30-day mortality across all patients with acute PE reported in the initial 45 papers selected for full-length review was 10%.

Two readers had perfect agreement on their choices of 10 retained full-length papers included in the outcome analysis (Kucher 2003[26], Geibel 2005[27],Toosi 2007[28], Kostrubiec 2009[29], Marchick 2009[30], Kukla 2011[31], Janata 2012[32], Kukla 2014[33], Agrawal 2014[34], Kukla 2015[35]). We also included data observed from a poster presentation (Hoechtl T, et al., 2009) to supplement Janata, et al, 2012. All studies had an adequate reference standard, ECG timing, ECG components and ECG results reported by outcomes. Table 3 shows the clinical features of the 3,007 patients contained in these 10 studies. The mean age was approximately 60 years and 57% of patients were female. The mortality ranged from 5 to 23% in those study populations included in the outcome analysis.

Prognostic value of ECG findings

Table 4 shows the main results, namely the pooled true positive rate and false positive rate for each ECG finding stratified by outcome. These pooled data showed a wide range of heterogeneity with I^2 and I^2_v ranging from 0% to 96%. The LR data in Table 4 were calculated with outcome negative patients considered disease free and either hemodynamic collapse or death considered disease positive. The LR values were calculated from the sensitivity and specificity values from the random effects model and included patients with either hemodynamic collapse or death as disease positive. These LR data suggest that six ECG findings can significantly alter prognosis of patients with PE (heart rate, S1Q3T3, cRBBB, inverted T waves in V1-V4, ST elevation in aVR, and atrial fibrillation), assuming that ECG findings with both an LR(-) value with upper limit 95% CI below unity and an LR(+) value with a lower limit 95% CI above unity modify the probability of hemodynamic collapse or death. Table 5 shows the odds ratios from the random effects model and corroborates the LR data regarding which ECG are significant predictors of hemodynamic collapse or death.

We then calculated the numeric Daniel score for patients, stratified by outcome. For this calculation, we included an additional study by Kline et al[36] that directly reported the Daniel score but not the results of the individual ECG components. The Shapiro Wilk test showed no evidence of non-normality (P=0.68). Table 6 shows these data and associated P values, indicating that patients who had hemodynamic collapse had significantly higher (5.9±3.9) scores than patients who were outcome negative (2.6±1.5, P=0.039, Dunnett's post-hoc), but patients' all-cause mortality did not have a significantly elevated Daniel score (4.9±3.3, P=0.12).

Publication bias

For the odds ratio data, the P values from Egger's tests indicated no evidence of publication bias for any of the three minimum required ECG criteria, heart rate > 100 beats/min, (P=0.401); S1Q3T3, (P=0.826);

or RBBB, (P=0.616), and funnel plots were symmetric. Figure 3 shows the funnel plot for RBBB. However, we also produced funnel plots, using the proportions of patients which were used to calculated the LR data in Table 4 (as opposed to the odds ratio) with each of the ECG criteria in Table 4, and these suggested possible publication bias for S1Q3T3 (P=0.007) and RBBB (P<0.001). In both cases, the shape of the funnel plots suggested that smaller studies tended to have higher proportions of patients with hemodynamic collapse or death with these two ECG findings.Sensitivity analysis

We recalculated the LR and OR data (using proportions calculated using the random effects model) after excluding one large study (Geibel et al). This study had a high risk of bias because it did not report ECG timing relative to death, did not report hemodynamic collapse and only reported heart rate, S1Q3T3 and RBBB. For the recalculated heart rate > 100 beats/min, the LR+ = 2.24 (1.88-2.58), and LR-= 0.33 (0.22-0.50) and OR = 6.58 (3.69-12.31); for S1Q3T3, the LR+ = 1.55 (1.26-1.88) and LR- = 0.84 (0.76-0.92) and the OR = 1.84 (1.35-2.49); for uRBBB, the LR+ = 1.73 (1.33-2.23), LR- = 0.91 (0.85-0.96), and OR = 1.90 (1.37-2.61); for cRBBB, the LR+ = 1.55 (0.90-2.61), LR-= 0.95 (0.87-1.01) and OR = 1.62 (0.81-3.04). Thus, exclusion of Geibel et al., reduced the significance of the LR and OR data for complete right bundle branch block.

Discussion

This systematic review and meta-analysis of 3,007 patients found six ECG findings (heart rate, S1Q3T3, cRBBB, inverted Twaves in V1-V4, ST elevation in aVR and atrial fibrillation) to predict either hemodynamic collapse or death within 30-days after acute PE. These six findings had significant LR values and odds ratios from the random effects model. Furthermore, calculation of the Daniel score, a previously derived 21-point ECG scoring system for severity of pulmonary hypertension from PE, was not significantly elevated in patients who died, but was significantly higher in patients who suffered hemodynamic collapse than those who were outcome negative. These findings were not surprising,

given that the majority of patients who die within 30 days after PE diagnosis succumb to other illness (e.g., cancer) whereas most patients who suffer hemodynamic collapse (or circulatory shock) have right ventricular failure. Although we cannot determine the exact timing of the hemodynamic collapse for all studies, prior registries found that 90% of patients who develop circulatory shock do so within 24 hours of diagnosis, and most in-hospital deaths directly attributed to PE occur within 48 hours of diagnosis.[37-41] Thus, we believe these ECG findings have relevance to decision-making for patients with PE in the ED setting. Taken together, these results suggest the validity of the individual components of the Daniel score and generally support the use of ECG in the risk-stratification of patients with acute PE.

The major strengths of this work include the pragmatic nature of the ECG and the large number of patients, confirming that several ECG components risk-stratify patients with PE. Indeed, several of the ECG components (particularly, heart rate, inverted T waves in leads V2 and V3, and ST elevation in aVR) had odds ratios higher than echocardiography findings of RV strain, an RV/LV ratio >0.9 on CT scanning, or an elevated troponin I concentration.[1] The value of this review for the practicing clinician comes from the fact that the ECG is woven into the standard workflow of evaluating patients with symptoms of PE, and is inexpensive, non-invasive and can diagnose alternative disease processes. Recent meta-analyses of clinical trials of fibrinolysis for intermediate risk PE have emphasized the need for careful patient selection both in terms of bleeding risk and risk of hemodynamic compensation.[42-44] Normotensive patients with low bleeding risk and high risk of hemodynamic decompensation from RV failure may benefit either systemic or catheter directed fibrinolysis. We submit that the six ECG findings provide a composite biomarker of RV failure, and thus provide specific bedside evidence of need for intensive care services and therapies known to reduce pulmonary arterial pressure, including systemic or catheter-based fibrinolysis, or possibly pulmonary selective vasodilation.[3, 45] Moreover, the pooled data show that a Daniel score should be used in the decision to evaluate a patient with PE for possible home treatment.[6, 46, 47] Our data suggest that a patient with PE and a Daniel ECG score >5, or ST elevation in

aVR or atrial fibrillation, should be considered to have a risk of hemodynamic collapse that is too high to safely allow home treatment, even if the patient is low-risk by other criteria.[7]

Limitations include the possibility that authors tended to be more likely to publish smaller papers that overrepresented the importance of an abnormal ECG in predicting a bad outcome from PE. However, neither the Egger's test nor the funnel plots for the odds ratio data for HR, S1Q3T3 and RBBB demonstrated evidence of publication bias. Another possible limitation of this study was the inconsistent reporting of all ECG criteria across the 45 papers selected for full-length review. Although all included papers were required to contain data on heart rate, S1Q3T3 and RBBB, variable reporting led to variable sample sizes of the other ECG findings of pulmonary hypertension. Other limitations include the definition and classification of specific ECG findings. First, most papers allowed no differentiation of the degree of T-wave inversion in leads V1 to V4. We therefore had to simplify all findings of T-wave inversion in leads V1 to V4 to a binary input of either present or absent. Studies were also inconsistent in the classification of RBBB. While some of the included studies categorized RBBB as either incomplete or complete, this was not always the case. We therefore created an "unspecified" group to include all RBBB findings (incomplete, complete and not stated). It is also possible that we could have missed relevant data or additional studies in our systematic search to include in this analysis. We attempted to minimize this risk by using broad search terms and emailing corresponding authors for additional data when necessary. It should also be noted that, given the nature of this review, we were unable to make any statement on the value of a completely normal ECG. We are unable to make any assessment about changes or timing of ECG. We were also unable to calculate summary receiver operating characteristic (SROC) curve for the Daniel score. Further, we graded study quality using the QUADAS-2 rather than QUIPs, which has also been used as a quality assessment instrument in prognostic SRs.[48] Finally, we wish to emphasize that the while atrial fibrillation with PE worsens

prognosis, this should not be taken to indicate that most patients with atrial fibrillation should have diagnostic testing for PE.[49]

Conclusion

This systematic review and meta-analysis demonstrates that six findings on 12-lead ECG that suggest RV strain from acute pulmonary hypertension, particularly sinus tachycardia, the S1Q3T3 pattern, RBBB, T wave inversions it V2-V3, ST elevation in AVR and atrial fibrillation, significantly increase the probability of circulatory shock and death from PE. A Daniel ECG score > 5 predicts increased probability of hemodynamic collapse. The 12 lead ECG should be used to risk-stratify patients with acute PE to make decisions about the need for advanced therapy or home treatment.

Contributors

JAK: Study concept and design, acquisition of the data, analysis and interpretation of the data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical expertise, administrative, technical, or material support, study supervision. He takes responsibility for the manuscript as a whole.

JDS, LKS, TWE: Acquisition of the data, analysis and interpretation, manuscript preparation, administrative, technical, and material support, study supervision.

Conflicts of interest

JAK is a consultant to Diagnostica Stago and has served on advisory boards to Genentech and Janssen, and has received research funding from the NIH and Ikaria.

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Figure 1. Daniel score for prediction of cardiac stress associated with acute pulmonary embolism. (Reproduced with permission Chest. 2001;120(2):474-481. doi:10.1378/chest.120.2.474

Figure 2. Prisma diagram of the selection process for papers.

Figure 3 Funnel plots for the odds ratio for RBBB (Egger's test P=0.616).