Estimation of acute pulmonary embolism pretest probability using electrocardiography and high sensitivity D-dimer test

PhD thesis

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1. Introduction

Worldwide, venous thromboembolism (VTE) is the third most common acute cardiovascular syndrome and one of the leading causes of cardiovascular death. In ageing developed countries, the annual incidence and the burden of healthcare due to VTE is increasing. In recent years, the prognosis of pulmonary embolism (PE) has improved partly due to overdiagnosis but probably mainly as a consequence of improved use of therapeutic options, stricter application of guidelines and because non-invasive imaging tests are more widely available. In the vast majority of cases, PE is suspected based on non-specific clinical signs and symptoms, which may suggest a broad spectrum of cardiopulmonary and other diseases, but a detailed investigation of PE in all such cases would be costly and potentially associated with adverse complications. Because PE is often fatal despite potentially mild initial symptoms, a diagnostic approach is needed that is specific enough to establish the need for anticoagulant treatment and sensitive enough to rule out PE with a rate of error of less than 2%. The guideline recommends a three-step assessment process for the diagnostic management of acute PE. First, the likelihood of it should be determined by either empiric clinical judgment, which may use electrocardiography (ECG) but has not been standardised to date or by validated prediction rules, which consider predisposing factors, symptoms, and clinical findings and are standardized but do not take ECG into account. After the pretest probability assessment, a D-dimer test should be performed in patients with a non-high pretest probability, and if positive, imaging should be used to confirm or exclude PE. Otherwise, although it does not give a thorough description of the reasons behind the recommendation, the guidelines do not consider high-sensitivity D-dimer testing safe and suggest imaging testing directly.

2. Objectives

Objective 1

To develop an ECG score as a tool in diagnosing acute pulmonary embolism, assess its performance in determining the pretest probability of pulmonary embolism and compare it with the most widely used prediction rules.

Objective 2

To assess whether a high-sensitivity D-dimer test can be used as a stand-alone test to exclude acute pulmonary embolism, independent of the pretest probability of acute pulmonary embolism as determined by clinical prediction rules

3. Methods

3.1. Retrospective pilot study

ECGs were collected from 136 patients treated at the 3rd Department of Internal Medicine of Semmelweis University and the Department of Cardiology, Saint Imre University Teaching Hospital, for confirmed PE between 2012 and 2017.

We developed an ECG score for the assessment of the pretest probability of acute PE by combining previously known morphological ECG signs representing the cardiac effects of the main pillars of the pathogenesis of acute PE. Namely, right ventricular dilatation from acute pulmonary arterial hypertension and consequent right ventricular ischemia and right-sided intraventricular conduction disturbances. Each ECG characteristic was considered to count for 1 point based on approximately equal importance. The ECG score was weighted to give more points if an ECG abnormality was observed in more than one typical lead and/or if more than one ECG abnormality was observed simultaneously in the lead.

The following ECG signs were included in the score:

- Primary ST elevation in aVR, in any of leads V1-3, in any of the inferior (II, III, aVF) leads,
- T wave inversion (i.e. negative T) in any of leads V1-3, in any of the inferior leads,
- QR or qR in V1,
- R/S> 1 in V1,
- Q wave in any of the inferior leads,
- novel incomplete or complete right bundle branch block,
- r' wave terminally in aVR,
- S1S2S3 syndrome,
- S wave in I, or in aVL, or any of leads V5-6 leads,
- slurring in the terminal part of the QRS or fragmented QRS in aVR, in any of leads V1-3 or any of the inferior leads.

A separate scoring was created for patients with right bundle branch block, where T wave inversion in precordial leads is secondary to intraventricular conduction disturbance and is not a primary abnormality.

From the individual ECG alterations, we constructed a four-step ECG score. A diagnosis of acute PE-unlikely was intuitively established with a score of less than 3, and an acute PE-likely was a score of 3 or more.

3.2. Prospective cohort

From November 2017 to October 2018, we included 149 consecutive patients at the 3rd Department of Medicine of Semmelweis University and the Saint Imre University Teaching Hospital, presenting with characteristic symptoms of acute PE: chest pain, dyspnea, collapse or syncope, and hemoptysis, who had an ECG with right-sided leads within 7 days of symptom onset. Data on the variables of the Wells and Geneva scores and imaging and relevant laboratory test results were extracted from the electronic medical records of each patient.

We added a fifth criterion to the ECG score, in which the presence of ST elevation or QS, QR morphologies in the right-sided chest leads was worth a further 1 point. This way, the maximum ECG score was 9 for patients with right bundle branch block (Table 2) and 10 for all others (Table 1**)**. Acute PE-likely diagnosis was established intuitively at ≥4.

Acute PE was considered confirmed or excluded based on the following: pulmonary CT angiography, lung scintigraphy and high-sensitivity ELISA D-dimer test. The D-dimer was also evaluated with a fixed cut-off (<500 μg/L) and an age-adjusted cut-off (<500 μg/L in subjects younger than 50 and age multiplied by 10 μg/L above 50). A 3-month follow-up was performed via telephone interviews for patients with excluded acute PEs based on the D-dimer test. Exclusion criteria were left bundle branch block on the ECG, persistent right ventricular pacemaker drive, and the underlying cause of the symptoms not identifiable. The ECGs of two patients could not be included in the ECG analysis, one due to the absence of evaluable right-sided leads and the other due to an atypical left bundle branch block. Thus, ECG scores were finally evaluated by two experts with extensive experience in ECG analysis, blinded to the diagnosis of PE in 147 patients using our ECG score and a previously existent ECG score for PE, the Daniel score. If the diagnoses made by the two specialists using each ECG score differed (22 cases with the new ECG score and 5 cases with the Daniel ECG score), the cases were re-evaluated. Discrepancies were resolved by consensus. Subsequently, we assessed the diagnostic value of the two types of ECG scores, the various Wells and Geneva scores, and the D-dimer test in the available cases to estimate the pretest probability of acute PE.

Table 1 Five-step ECG scoring sheet for patients without right bundle branch block

	ECG signs		**points**
1	S1QinferiorTinferior or S1+T wave inversion in leads V1-3	If any two are present simultaneously	1
		If three are present simultaneously	2
2	Primary ST-segment elevation in the inferior leads and/or lead aVR and/or leads V1-3 or T wave inversion in the inferior leads and/or leads V1-3	Either ST elevation or T wave inversion in one of the locations	1
		Either ST elevation or T wave inversion in 2 or more of the locations OR both ST elevation and T wave inversion in one location	2
		ST elevation in 2 or more of the locations and T wave inversion in one location OR ST elevation in one location and T wave inversion in 2 or more of the locations	3
		Both ST elevation and T inversion in 2 or more locations	4
3	QR or qR complexes or R/S>1 in lead V1	If any present	1
4	Terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 and /or fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	If only terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 OR only fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	1
		If terminal r' wave in lead aVR and/ or S1S2S3 syndrome and/or S wave in leads aVL, V4-6 AND fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	2
5	Primary ST-segment elevation and/or QS or QR complexes in leads RV4-6	If present	1

Table 2 Five-step ECG scoring sheet for patients with right bundle branch block

	ECG signs		**points**
1	Qinferior or primary Tinferior	If either present	1
		If both are present simultaneously	2
2	Primary ST-segment elevation in the inferior leads and/or lead aVR and/or leads V1-3 or T wave inversion in the inferior leads	Either ST elevation or T wave inversion in one of the locations	1
		ST elevation and T wave inversion in the inferior leads OR ST elevation in 2 or more of the locations	2
		ST elevation in 2 or more locations and T inversion	3
3	QR or qR complexes in lead V1	If any present	1
4	Proven new RBBB and/or fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	If only new RBBB OR only fragmented or slurred QRS complexes in lead aVR, leads V1-3 and/or inferior leads	1
		If new RBBB AND fragmented or slurred QRS complexes in lead aVR and/or in leads V1-3 and/or inferior leads	2
5	Primary ST-segment elevation and/or QS or QR complexes in leads RV4-6	If present	1

3.3. Retrospective study of pretest probability evaluation with our modified ECG score and high sensitivity D-dimer test

Third, we conducted a retrospective study of 1270 consecutive patients with no current anticoagulation treatment undergoing CT angiography at the Emergency Department of the Saint Imre University Teaching Hospital between March 2020 and July 2021 for suspected acute PE presented with its characteristic symptoms and complaints. The medical records of all patients were reviewed, and the CT scan results, the parameters corresponding to each criterion of the Wells scores and Geneva scores, the D-dimer results and their electrocardiograms, if available, taken within 7 days of the onset of symptoms, were individually extracted. Patients with a negative D-dimer test result were followed up for 3 months for possible VTE events. Those rehospitalized during this time by reviewing their patient records and the others by telephone interview. Of the 1270 patients, 925 patients had a D-dimer test available.

The 120 patients with negative D-dimer test results and the first consecutive 225 D-dimer positive patients were evaluated to determine the pretest probability of acute PE by different Wells scores and Geneva scores. We also determined the pretest probability of acute PE using a modified version of the new ECG score we developed previously, from which we had to omit criterion 5 since the right-sided chest leads were not available in most cases. Compensating for this, we have included two additional, previously unused ECG signs in criterion 3 instead worth one point each if they were present: low voltage, defined as the maximum peak-to-peak QRS amplitude not exceeding 0.5 mV in either limb lead, and R/S ratio <1 in the V5 lead. Further modifications were made as follows: if T negativity was present in the inferior or V1-3 leads with an S wave in lead I, or if inferior T wave negativity was associated with an inferior Q wave, it was only considered in criterion 1 but not in step 2. We have also created a separate

modified scoring system for patients with right bundle branch block. Acute PE was diagnosed at ≥5/9 for patients with right bundle branch block and ≥6/10 for all others. Exclusion criteria included left bundle branch block and ventricular pacemaker rhythm. Out of 345 patients, 100 D-dimer negative and 206 D-dimer positive, a total of 306 patients had ECG tracings of adequate quality available for analysis. The patients' ECGs were analyzed using the modified ECG score the same way and by the same two experts as in the previous study. CT angiography was performed with a 256 Slice GE Revolution CT scanner. D-dimer tests were performed by a high-sensitivity latex-enhanced immunoturbidimetric assay. According to the manufacturer's recommendation, test results were negative if they were below <500 μgFEU/L in subjects younger than 50 and below the age-adjusted D-dimer cut-off value (age multiplied by 10 in μgFEU/L) in all other subjects.

Statistical analysis

A $p<0.05$ value was considered statistically significant. GraphPadPrism version 6 for Windows (GraphPad Software Inc., La Jolla, CA, USA) was used to calculate and compare sensitivity, specificity and predictive values. N-1 $\chi 2$ test was applied without adjustment for multiple comparisons. Patient characteristics were compared with Fisher's exact test. In case of +LR and -LR, statistical significance was concluded if 95% confidence intervals did not overlap. IBM SPSS Statistics 25 for Windows software package (IBM Corp. Armonk, NY, USA) was used for measuring interobserver variability by kappa statistics. The overall interobserver agreement was categorized as follows: as near complete if $\kappa > 0.8$, good if $\kappa = 0.61$ to 0.8, moderate if $\kappa = 0.41$ to 0.6, fair if $\kappa = 0.21$ to 0.4 and poor if $\kappa < 0.2$.

4. Results

4.1. Retrospective pilot study

We have found a test accuracy (TA) of 87.5% (119 correct diagnoses/ 136 total cases) in the retrospective pilot cohort. The score gave a correct diagnosis in all 27 cases of massive PE, 40 of 46 cases of PE (87%) and 52 of 63 cases of peripheral PE (82.5%).

4.2. Prospective cohort

Out of the 149 patients, acute PE was excluded in 73 and confirmed in 76. None of the 25 patients with a negative D-dimer test to exclude PE had a VTE event during follow-up. The sensitivity (SE) and the negative predictive value (NPV) of the D-dimer test alone was 100%, and the negative likelihood ratio ((-) LR) was 0 with both cut-off values. A positive diagnosis based on our score indicated the true positivity of the D-dimer test similar to the Wells score and superior to the Geneva scores and Daniel score. The overall performance of our ECG score was better than the other scores' or D-dimer testing, with a TA of 84.4%. It was superior in regards of the rate of false negative diagnoses (2%), SE (98.7%), NPV (98%) and (-)LR (0.019) to all other scores and in level with the D-dimer. It was significantly superior to the Geneva scores and the D-dimer test but not the Daniel or Wells scores regarding positive predictive value (PPV). The specificity (SP) (69%) of our ECG score was lower than the Daniel score's and Wells scores', similar to the revised, simplified Geneva score's, but higher than the revised Geneva score's and the D-dimer test's. Interobserver agreement was lower with our ECG score (κ: 0.701) than with the Daniel score (κ: 0.934).

4.3 Retrospective study of pretest probability evaluation with our modified ECG score and high-sensitivity D-dimer test

4.3.1. Performance of the scores in the whole group

When applying the ECG score, we found a good interobserver agreement (κ = 0.748). The modified ECG score was significantly better than the other scores regarding SP (96%) and PPV (66.7%). The Geneva score showed a significantly higher SE (48.4% vs ECG score 35.7%). The positive likelihood ratio ((+)LR) of the ECG score (8.93) was higher than that of the Geneva score and did not differ significantly from the Wells score's. There was no difference in regard of the (-)LR and the NPV between the scores; all NPV-s were higher than 86%. The TA of the ECG score (85%) was significantly higher than that of the Geneva score but not than that of the Wells score.

4.3.2. Comparison of the performance of each score in D-dimer negative patients

We have found 1 case of acute PE out of 120 D-dimer-negative patients. Regarding TA, the ECG score and the Wells score had similar values, both being significantly higher than the Geneva score's (98% and 92.5%, respectively, vs 76.7%, $p<0.001$ for both). Its SP was 99%, and the NPV value was 98.7%. Among the metrics, only the SP and NPV of the different were comparable by statistical analysis because the SE, PPV, and (+)LR of the ECG score were 0 due to the 0 true positive diagnoses. The (−)LRs of the Wells and Geneva scores were 0 due to their 0 false negative diagnosis, and consequently, their SEs and NPVs were 100 %. The SP of the Wells score and the Geneva score were both lower (92.4% and 76.5%, $p< 0.05$), with a significant difference between the two ($p<0.001$). The Wells score had a higher (+)LR than the Geneva score.

Thromboembolic events did not occur in any of the patients during the 3-month follow-up.

4.3.4. Comparison of the performance of each score in D-dimer positive patients

The ECG and the Wells scores had higher TA than the Geneva score (78.6 % and 75.1% vs 64.9%, $p<0.01$ and $p<0.05$, respectively). The ECG score had a higher PPV than both other scores (69% vs 48.1% and 38.2%, $p<0.001$ for both). Its SE was higher compared to the Wells score but lower than the Geneva score (36.4%, 23.6% and 47.5%, respectively, $p<0.05$). The SP of the ECG score and the Wells score were higher than the Geneva score's (94%, 91.48% and 71.3%, $p<0.00$). There was a significant difference in the (+)LR between the ECG and Geneva score. The NPV predictive value and (-)LR were similar with all the scores.

4. Conclusions

1. Through careful selection and combination of ECG abnormalities that best reflect the main cardiac pathophysiological components of acute pulmonary embolism, a bedside usable score system has been developed that is free of subjectivity and thus standardizable, making electrocardiography an established tool in diagnosing acute pulmonary embolism not only in identifying severe cases but also in assessing pretest probability and exclusion.

2. Due to the superiority in sensitivity, negative predictive value, test accuracy and negative likelihood ratio, the diagnostic accuracy of our ECG score is superior to the Daniel ECG score and prediction rules endorsed by the current ESC guidelines for determining the pretest probability of acute pulmonary embolism.

3. In our population sample, a high-sensitivity D-dimer test could be safely used as a stand-alone test to exclude acute pulmonary embolism among symptomatic emergency department patients, not on anticoagulant treatment independent of the pretest probability of acute pulmonary embolism as determined by clinical prediction rules.

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