Differences in Negative T Waves Between Acute Pulmonary Embolism and Acute Coronary Syndrome

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**Background:** Patients with acute pulmonary embolism (APE) often have negative T waves (Neg T) in precordial leads at presentation, but this is also found in acute coronary syndrome (ACS) caused by left anterior descending coronary artery (LAD) disease.

**Methods and Results:** Differences in Neg T on admission electrocardiograms were studied between 107 patients with APE and 248 patients with ACS caused by LAD disease. All patients had Neg T in leads V1–4 and were admitted within 7 days from symptom onset. The number of leads with Neg T (4.8±1.8 vs. 5.5±1.7, P<0.001) and maximum magnitude of Neg T (3.4±2.0 vs. 4.7±3.3 mm, P<0.001) were lower in APE. The frequency of occurrence of Neg T in each of the 12 leads, and the precordial lead with the greatest Neg T (peak Neg T) differed between APE and ACS (all P<0.05, respectively). APE was strongly associated with the presence of Neg T in both leads III and V1 and peak Neg T in leads V1–2. The combination of these 2 findings identified APE with 98% sensitivity, 92% specificity, and 94% predictive accuracy, which represented the highest diagnostic accuracy.

**Conclusions:** Among patients with APE and ACS who have precordial Neg T, the presence of Neg T in leads III and V1 and/or peak Neg T in leads V1–2 simply but accurately differentiates APE from ACS.

**Key Words:** Acute coronary syndrome; Electrocardiogram; Pulmonary embolism

Acute pulmonary embolism (APE) is a potentially fatal disease.1–4 In a large multicenter trial of APE, most deaths from pulmonary embolism occurred within the first week after study entry, and the main cause of death was recurrence of pulmonary embolism.2 But if APE is promptly diagnosed and appropriately treated, recurrence of pulmonary embolism is rare and death is uncommon, excluding patients who initially present with hemodynamic impairment.1 The diagnosis of APE relies predominantly on the degree of clinical suspicion. The electrocardiogram (ECG), generally the first diagnostic examination performed, is of limited value for the diagnosis of APE per se, but can help to identify patients at high risk for adverse outcomes. Patients with severe APE often have negative T waves (Neg T) in precordial leads on ECG,5–12 but this ECG finding also occurs in patients with acute coronary syndrome (ACS) caused by critical stenosis of the left anterior descending coronary artery (LAD).7,8,13–15 Symptoms of APE, such as chest pain/discomfort or dyspnea, are often difficult to differentiate from those of ACS.1,10,16 In addition, serum cardiac troponin level, a well-known diagnostic marker of myocardial ischemia in ACS,13 has been shown to be elevated in patients with severe APE.5,17,18 Prompt differentiation between these 2 diseases is essential for selecting the appropriate treatment strategy and improving outcome. Echocardiography is likely to be useful for differential diagnosis between APE and ACS; however, the results of echocardiographic evaluation are not always readily available at the time of clinical presentation. We previously studied ECG differences between patients with ACS and APE who had Neg T in precordial leads.7,8 The distributions of Neg T differed between APE and ACS, and the presence of Neg T in both leads III and V1 was useful for differentiating APE from ACS. The sensitivity of this approach, however, was 88%, and differential diagnosis of APE was not possible in some patients.7 Misdiagnosis of APE as ACS has been shown to be linked to preventable deaths in patients with APE.1,16 The objective of this study was to further identify differences in Neg T between APE and ACS in patients who presented with precordial Neg T. The ultimate goal was to identify ECG criteria with higher sensitivity for the differential diagnosis of APE than that in our previous studies and thereby more accurately differentiate APE from ACS.
Patients
We retrospectively studied 355 consecutive patients (107 patients with APE and 248 with ACS) who were admitted to our coronary care unit within 7 days from symptom onset between May 1998 and March 2013 and who fulfilled the following criteria: (1) no conditions precluding the evaluation of ST-T changes on ECG (ie, complete left or right bundle-branch block, left ventricular hypertrophy, ventricular pacing, or receiving drugs with potential effects on ST-T changes); (2) no obvious past history of cardiopulmonary disease; and (3) fully assessable ECG on admission with Neg T ≥2.5 mm in 2 or more precordial leads (V1–4). Patients with ST-segment elevation (deviation in leads V2–3, ≥2.0 mm in men aged ≥40 years, ≥2.5 mm in men aged <40 years, or ≥1.5 mm in women; or deviation ≥1.0 mm in ≥2 other contiguous leads) on admission ECG were excluded.19 The study was approved by the Ethics Committee of our institution, and all subjects gave informed consent.

APE Group Patients who had symptoms suggesting APE, such as acute onset of dyspnea, chest pain/discomfort, palpitations, or syncope were studied. The diagnosis of APE was confirmed by 1 or more of the following examinations: contrast-enhanced computed tomography (n=87), pulmonary angiography (n=44), or lung perfusion scintigraphy (n=73). Twenty-four patients were positive for APE on all 3 examinations, and 49 were positive on 2 examinations. Right ventricular dysfunction was diagnosed if patients had any of the following findings on transthoracic echocardiography: (1) abnormal motion of the interventricular septum; (2) dilation of the right ventricle (diastolic diameter ≥30 mm) or a right/left ventricle diameter ratio ≥1.0; (3) hypokinesia of the right ventricle; or (4) tricuspid valve regurgitation (jet velocity >2.5 m/s).17,18

ACS Group Patients who had an unstable pattern of symptoms suggested to be caused by cardiac ischemia (including rest, new onset, or increasing angina) were studied.13 Coronary angiography was performed during hospitalization, and stenosis ≥75% in 1 or more major epicardial vessels or their main branches was considered clinically significant. The presence of the most severe stenosis, intracoronary thrombus, or both, in LAD was documented in all patients.

ECG Evaluation
On admission, 12-lead ECGs were recorded at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The anatomically contiguous Cabrera sequence (III, aVl, II, –aVr, I, and aVl) was used to display limb leads, as recommended in current international recommendations for the clinical interpretation of ECG.14 All ECGs were examined by a single cardiologist who was blinded to all other clinical data. ST-segment deviation was measured manually to the nearest 0.5 mm at the J point.14 ST-segment depression was considered present if ST-segment was horizontal or down-sloping and the deviation was at least 0.5 mm, and Neg T was considered present if the depth was at least 1.0 mm. We examined not only the distribution of Neg T, but also that of peak Neg T, that is, the precordial lead with the greatest Neg T. We also analyzed the following ECG findings, previously shown to be associated with APE:5–9 (1) P pulmonale (P waves with amplitudes ≥2.5 mm in limb leads or >1.5 mm in lead V1); (2) right axis deviation (QRS electrical axis >90°); (3) left axis deviation (QRS electrical axis ≤−30°); (4) S1S3S1 pattern (presence of S waves with amplitudes ≥1.5 mm in leads I, II, and III); (5) S1S3Q1T1 pattern (presence of S waves in lead I and Q waves in lead III, each having amplitudes >1.5 mm, in association with Neg T in lead III); (6) low voltage (greatest overall deflection of QRS complex ≤5.0 mm in all limb leads); and (7) clockwise rotation (a shift in the transition zone [R=S] in the precordial leads to V3 or beyond).

Cardiac Enzyme Measurement
Cardiac-specific troponin T or I was measured on admission, and was defined as positive for a level ≥0.1 ng/ml.

Statistical Analysis
Continuous data are expressed as mean±SD, and categorical data are expressed as numbers and percentages. Unpaired Student’s t-test or the Mann-Whitney U-test was used to compare continuous variables. Chi-squared test was used to compare categorical variables. Differences were considered statistically significant at P<0.05. The data were analyzed using SPSS, version 20.0 (SPSS, Chicago, IL, USA).

Results
Baseline characteristics are listed in Table 1. Patients with APE were younger and less likely to be men and had a lower systolic blood pressure and a more rapid heart rate on admission, and lower rates of diabetes mellitus, hypertension, hyperlipidemia, and smoking than patients with ACS. Other characteristics did not differ between APE and ACS. In patients with APE, 81% had right ventricular dysfunction. In patients with ACS, 37.5% had multivessel disease (29% had 2-vessel dis-

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
<th>APE (n=107)</th>
<th>ACS (n=248)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>64±13</td>
<td>68±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men</td>
<td>38 (36)</td>
<td>148 (60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission ≤24 h from symptom onset</td>
<td>72 (67)</td>
<td>185 (75)</td>
<td>0.16</td>
</tr>
<tr>
<td>SBP on admission (mmHg)</td>
<td>124±25</td>
<td>152±26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate on admission (beats/min)</td>
<td>94±19</td>
<td>70±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9 (8)</td>
<td>62 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45 (42)</td>
<td>152 (61)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>11 (10)</td>
<td>100 (40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>13 (12)</td>
<td>114 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive troponin on admission1</td>
<td>42/88 (48)</td>
<td>113 (46)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). *Available for 88 patients with APE. ACS, acute coronary syndrome; APE, acute pulmonary embolism; SBP, systolic blood pressure.
ST-segment depression and number and maximum amplitude of Neg T were lower in APE. The distribution of Neg T is shown in Figure 1. The frequency of Neg T significantly differed between APE and ACS in each of 12 leads. In limb leads, the prevalence of Neg T gradually decreased from leads III to –aVR, and Neg T was not found in lead I or aVL in APE, whereas Neg T was frequently observed in leads I and aVL, particularly in leads 7 and 8.5% had 3-vessel disease). Severe stenosis $\geq 90\%$ of LAD was observed in 76%.

ECG findings on admission are presented in Table 2. APE was more frequently associated with right axis deviation, S1S2S3 and S1Q3T3 patterns, low voltage, and clockwise rotation. The frequencies of P pulmonale and left axis deviation did not differ between APE and ACS. The frequency and magnitude of ST-segment depression and number and maximum amplitude of Neg T were lower in APE. The distribution of Neg T is shown in Figure 1. The frequency of Neg T significantly differed between APE and ACS in each of 12 leads. In limb leads, the prevalence of Neg T gradually decreased from leads III to –aVR, and Neg T was not found in lead I or aVL in APE, whereas Neg T was frequently observed in leads I and aVL, particularly in

<table>
<thead>
<tr>
<th>Electrocardiographic Findings</th>
<th>APE (n=107)</th>
<th>ACS (n=248)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P pulmonale</td>
<td>8 (8)</td>
<td>8 (3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Right axis deviation</td>
<td>6 (6)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left axis deviation</td>
<td>8 (8)</td>
<td>14 (6)</td>
<td>0.51</td>
</tr>
<tr>
<td>S1S2S3 pattern</td>
<td>12 (11)</td>
<td>3 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S1Q3T3 pattern</td>
<td>24 (22)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low voltage</td>
<td>26 (24)</td>
<td>10 (4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clockwise rotation</td>
<td>23 (22)</td>
<td>1 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>39 (36)</td>
<td>139 (56)</td>
<td>0.001</td>
</tr>
<tr>
<td>Summed ST-segment depression (mm)</td>
<td>1.0±2.1</td>
<td>1.9±2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>No. leads with Neg T</td>
<td>4.8±1.8</td>
<td>5.5±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximum magnitude of Neg T (mm)</td>
<td>3.4±2.0</td>
<td>4.7±3.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). Neg T, negative T wave. Other abbreviations as in Table 1.

**Figure 1.** Distribution of negative T waves (Neg T) in patients with acute pulmonary embolism (APE) and acute coronary syndrome (ACS). *P<0.05, **P<0.01 vs. ACS.

**Figure 2.** Magnitude of negative T waves (Neg T) in patients with acute pulmonary embolism (APE) and acute coronary syndrome (ACS). *P<0.05, **P<0.01 vs. ACS.
This study examined differences in ECG findings, particularly Neg T, between patients with APE and ACS caused by LAD disease who presented with precordial Neg T, with the ultimate goal of determining whether such differences would facilitate differential diagnosis. We have previously shown that the presence of Neg T in leads III and V1 was useful for differentiating APE from ACS in patients who had precordial Neg T.

In the present study, this ECG criterion likewise strongly suggested APE, but, consistent with the results of our previous studies, the presence of Neg T in leads III and V1 failed to differentiate APE in approximately 10% of the patients. We therefore newly evaluated peak Neg T, which we did not assess previously. The present study showed that the distribution of peak Neg T clearly differed between APE and ACS: the occurrence of peak Neg T was most frequent in leads V1–2 in APE and leads V3–4 in ACS. To our best knowledge, this is the first study to examine peak Neg T in patients with APE and ACS. Peak Neg T in leads V1–2 as well as the presence of Neg T in leads III and V1 had high predictive value for APE. The majority (76%) of patients with APE had these 2 findings, but some patients (22%) had either finding alone. By combining these 2 findings, we could improve the sensitivity and negative predictive value for identifying APE. The present results confirm and extend our finding that the latter, and was rare in inferior leads and lead –aVR in ACS.

In precordial leads, Neg T was consistently observed in leads V1–2, and the prevalence of Neg T gradually decreased from leads V3 to V6 in APE, whereas the distribution of Neg T centered around leads V2–4 in ACS. Neg T magnitude is shown in Figure 2. The magnitude of Neg T significantly differed between APE and ACS in 11 leads, excluding lead V2, and was greatest in leads V1–2 in APE and leads V3–4 in ACS. Figure 3 shows the distribution of peak Neg T, that is, the precordial lead with the greatest Neg T. Peak Neg T was found mainly in leads V1–2 in APE and in leads V3–4 in ACS.

The presence of Neg T in both leads III and V1 and peak Neg T in leads V1–2 was most strongly associated with APE among all ECG findings. Among 107 patients with APE, 81 (76%) had both of these 2 findings, whereas 24 (22%) had each finding alone. Table 3 lists the ECG findings for identifying APE. These 2 ECG findings had high similar predictive value for APE. When these 2 ECG findings were combined (ie, the presence of Neg T in lead III and V1, peak Neg T in leads V1–2, or both), the sensitivity and negative predictive value significantly improved, as compared with each finding alone. The other predictive values were similar to those of either criterion alone. Figures 4,5 show representative ECGs.

**Figure 3.** Distribution of the precordial lead with the greatest negative T waves (peak Neg T) in patients with acute pulmonary embolism (APE) and acute coronary syndrome (ACS). *P<0.05, **P<0.01 vs. ACS. Among patients with APE, the magnitude of Neg T was the same in leads V1 and V2 in 4 patients, leads V2 and V3 in 4 patients, and leads V1 and V4 in 2 patients. The data for these patients are not included in the figure. Among patients with ACS, the magnitude of Neg T was the same in leads V1 and V3 in 1 patient, leads V2 and V4 in 16 patients, and leads V3 and V4 in 8 patients. The data for these patients are not included in the figure.

**Table 3.** ECG Markers for Identifying APE

<table>
<thead>
<tr>
<th>Presence of Neg T in leads III and V1 and/or peak Neg T in leads V1–2</th>
<th>Presence of Neg T in leads III and V1</th>
<th>Peak Neg T in leads V1–2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>98</td>
<td>87**</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>83</td>
<td>89</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>99</td>
<td>94**</td>
</tr>
<tr>
<td>Predictive accuracy (%)</td>
<td>94</td>
<td>93</td>
</tr>
</tbody>
</table>

**P<0.01 vs. the presence of Neg T in leads III and V1 and/or peak Neg T in leads V1–2. Peak Neg T in leads V1–2 was considered to be present if the magnitude of Neg T was the same in leads V1 and V2, and absent if the magnitude of Neg T was the same in leads V2 and V3.

ECG, electrocardiogram. Other abbreviations as in Tables 1,2.

**Discussion**

This study examined differences in ECG findings, particularly Neg T, between patients with APE and ACS caused by LAD disease who presented with precordial Neg T, with the ultimate goal of determining whether such differences would facilitate differential diagnosis. We have previously shown that the presence of Neg T in leads III and V1 was useful for differentiating APE from ACS in patients who had precordial Neg T. In the present study, this ECG criterion likewise strongly suggested APE, but, consistent with the results of our previous studies, the presence of Neg T in leads III and V1 failed to differentiate APE in approximately 10% of the patients. We therefore newly evaluated peak Neg T, which we did not assess previously. The present study showed that the distribution of peak Neg T clearly differed between APE and ACS: the occurrence of peak Neg T was most frequent in leads V1–2 in APE and leads V3–4 in ACS. To our best knowledge, this is the first study to examine peak Neg T in patients with APE and ACS. Peak Neg T in leads V1–2 as well as the presence of Neg T in leads III and V1 had high predictive value for APE. The majority (76%) of patients with APE had these 2 findings, but some patients (22%) had either finding alone. By combining these 2 findings, we could improve the sensitivity and negative predictive value for identifying APE. The present results confirm and extend our previous findings.
ECG Differentiation Between APE and ACS

was very low. These findings may be attributed to the fact that
the perfusion territory of LAD does not usually extend to the
regions faced by these leads.

In APE, ECG abnormalities such as P pulmonale, right and
left axis deviation, S1 S2 S3 and S1 Q 3 T 3 patterns, low voltage,
and clockwise rotation have been shown to be highly variable
and frequently transient.

In the present study, these findings
were more often found in APE than in ACS, but the frequency
of occurrence was low, indicating specificity, but not sensitivity
for APE. In contrast, Neg T is known to be the most common,
persistent change in APE.

Previous studies have suggested
that severe ischemia of the right ventricle may result from an
acute right ventricular pressure overload, impaired coronary
blood flow, and hypoxia caused by APE, possibly leading to
Neg T.

In the present study, Neg T in leads III and V1–2 was
very common in APE, and peak Neg T was also mainly found
in leads V1–2. Lead III faces the inferior region of the right ven-
tricle, and leads V 1 and V 2 face the anterior region of the right
ventricle. With increasing severity of right heart failure and
dilation of the right ventricle towards the left, Neg T is thought

The mechanisms responsible for the different distributions
of Neg T and peak Neg T in APE and ACS are uncertain, but
may involve differences in underlying electrophysiologic con-
ditions between these 2 diseases. In ACS, the ischemia-related
artery and its perfusion territory can be predicted on the basis
of the distribution of Neg T.7,8,20 In patients with ACS caused
by LAD disease, Neg T was distributed primarily around lead
aVl in limb leads and leads V 2–4 in precordial leads, facing the
lateral region and the anterior region of the left ventricle, re-
spectively. Peak Neg T was also mainly found in leads V 1–4.

Among patients with ACS in the present study, 67% had Neg
T in lead V 1, facing the right paraseptal region, probably due
to more proximal LAD disease,21,22 and 58% had Neg T in leads
V 2–6, facing the posterolateral wall adjacent to the apex of the
left ventricle, probably due to LAD disease involving a large
diagonal branch. Conversely, the frequency of occurrence of
Neg T in lead –aV 6 and inferior leads, which face the apical
region14 and the inferior wall of left ventricle, respectively,
to move towards the left, that is, from leads III to aVf to II in limb leads and from leads V1 to V6 in precordial leads. Neg T was rare in leads –aVR and V5–6 and was not found in leads I or aVL. These findings are ascribed to the fact that dilation of the right ventricle in APE rarely extends to the regions faced by these leads.

The 12-lead ECG is a simple, prompt, inexpensive, and widely used initial clinical diagnostic examination. Our proposed simple ECG criteria can be used for diagnosis in most physicians’ practices to help raise the suspicion of APE and indicate the need for further tests to establish a definitive diagnosis.

Study Limitations
This study was retrospective and performed at a single center. Furthermore, great caution is required because we studied only patients who presented with precordial Neg T and were found to have APE or ACS caused by LAD disease to ensure a homogeneous group of subjects. Regardless of the limited study group, however, the present subjects were at high risk, making early and accurate diagnosis and treatment essential for improved outcome. Further prospective studies in larger numbers of patients are required to confirm the present findings.

Conclusions
Among patients with APE and ACS who have precordial Neg T, the presence of Neg T in leads III and V1 and/or peak Neg T in leads V1–2 simply but accurately differentiates APE from ACS.

References