Electrocardiographic Differentiation of Early Repolarization From Subtle Anterior ST-Segment Elevation Myocardial Infarction

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Study objective: Anterior ST-segment elevation myocardial infarction (STEMI) can be difficult to differentiate from early repolarization on the ECG. We hypothesize that, in addition to ST-segment elevation, T-wave amplitude to R-wave amplitude ratio (T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$), and R-wave amplitude in leads V2 to V4, computerized corrected QT interval (QTc) and upward concavity would help to differentiate the 2. We seek to determine which ECG measurements best distinguish STEMI versus early repolarization.

Methods: This was a retrospective study of patients with anterior STEMI (2003 to 2009) and early repolarization (2003 to 2005) at 2 urban hospitals, one of which (Minneapolis Heart Institute) receives 500 STEMI patients per year. We compared the ECGs of nonobvious ("subtle") anterior STEMI with emergency department noncardiac chest pain patients with early repolarization. ST-segment elevation at the J point and 60 ms after the J point, T-wave amplitude, R-wave amplitude, QTc, upward concavity, J-wave notching, and T waves in V1 and V6 were measured. Multivariate logistic regression modeling was used to identify ECG measurements independently predictive of STEMI versus early repolarization in a derivation group and was subsequently validated in a separate group.

Results: Of 355 anterior STEMIs identified, 143 were nonobvious, or subtle, compared with 171 early repolarization ECGs. ST-segment elevation was greater, R-wave amplitude lower, and T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$ higher in leads V2 to V4 with STEMI versus early repolarization. Computerized QTc was also significantly longer with STEMI versus early repolarization. T-wave amplitude did not differ significantly between the groups, such that the T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$ difference was entirely due to the difference in R-wave amplitude. An ECG criterion based on 3 measurements (R-wave amplitude in lead V4, ST-segment elevation 60 ms after J-point in lead V3, and QTc) was derived and validated for differentiating STEMI versus early repolarization, such that if the value of the equation ([1.196 x ST-segment elevation 60 ms after the J point in lead V3 in mm]+[0.059 x QTc in ms]–[0.326 x R-wave amplitude in lead V4 in mm]) is greater than 23.4 predicted STEMI and if less than or equal to 23.4, it predicted early repolarization in both groups, with overall sensitivity, specificity, and accuracy of 86% (95% confidence interval [CI] 79, 91), 91% (95% CI 85, 95), and 88% (95% CI 84, 92), respectively, with positive likelihood ratio 9.2 (95% CI 8.5 to 10) and negative likelihood ratio 0.1 (95% CI 0.08 to 0.3). Upward concavity, upright T wave in V1 or T wave, in V1 greater than T wave in V6, and J-wave notching did not provide important information.

Conclusion: R-wave amplitude is lower, ST-segment elevation greater, and QTc longer for subtle anterior STEMI versus early repolarization. In combination with other clinical data, this derived and validated ECG equation could be an important adjunct in the diagnosis of anterior STEMI. [Ann Emerg Med. 2012;60:45-56.]

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Editor's Capsule Summary

What is already known on this topic

The differentiation of anterior ST-segment elevation myocardial infarction (STEMI) from early repolarization on ECG can be challenging.

What question this study addressed

This retrospective cohort study identified ECG characteristics with the highest utility for differentiating anterior STEMI from early repolarization, and an ECG criterion was developed (N=130) and validated (N=184).

What this study adds to our knowledge

The 3 predictors included in an ECG criterion with 88% accuracy were R-wave amplitude in lead V4, ST-segment elevation at 60 milliseconds after the J point in V3, and QTc.

How this is relevant to clinical practice

If validated in subsequent studies, this rule could be incorporated into computerized ECG analysis algorithms to further assist physicians in this important, difficult task.

INTRODUCTION

Background and Importance

Rapid diagnosis of ST-segment elevation myocardial infarction (STEMI) is critical to initiate timely reperfusion therapy. However, there are several conditions with electrocardiographic ST-segment elevation that can mimic STEMI.[1] These "pseudoinfarction patterns" include, among others, early repolarization. Early repolarization in the anterior precordial leads has come to be synonymous with a normal baseline ECG result that manifests ST-segment elevation in leads V2 to V4.

The 2 entities may be difficult to distinguish from each other for several reasons. First, upward ST-segment concavity, usually associated with normal ECG results,[1] is also present in 30% to 40% of anterior STEMI (due to left anterior descending artery occlusion), especially early after onset of symptoms.[2,3] Moreover, 30% to 40% of anterior STEMIs have borderline ST-segment elevation (absence of 2 consecutive leads with at least 2 mm of ST-segment elevation), and 20% may have upward concavity and borderline ST-segment elevation.[3] Conversely, most benign ECGs have at least 1 mm of ST-segment elevation in right precordial leads.[4,5] Thus, specific ECG criteria distinguishing STEMI from early repolarization would be useful when making the reperfusion decision.

There is significant evidence that physicians have a difficult time differentiating normal ST-segment elevation from STEMI. Larson et al[6] found that 187 (14%) of 1,335 patients referred for primary percutaneous coronary intervention did not have a culprit lesion; 25 of these were "early repolarization" and 20 were "nondiagnostic" ST-segment elevation. In another study, 76% of catheterization laboratory activations were "true STEMI."[7] "Non-STEMIs" later identified as missed occlusions were not tabulated. The authors cited a 5% inappropriate activation rate (STEMI activation was called "appropriate" even if the patient ultimately received a diagnosis of non-STEMI and did not actually need emergency reperfusion). Two other studies found that 8% and 11% of patients referred for primary percutaneous coronary intervention for anterior STEMI had completely normal coronary arteries.[8,9] Brady[10] studied 902 patients with chest pain: 85% did not have a final diagnosis of acute myocardial infarction. From this group, there were 2 false-negative and 10 false-positive ECG readings for STEMI. Left ventricular aneurysm and early repolarization were the most commonly misdiagnosed entities.[11] In another study, Brady et al[12] studied 599 consecutive chest pain patients; 212 (35%) had ST-segment elevation, and of these, only 55 (26%) had acute myocardial infarction. Of the 157 patients without myocardial infarction, there were 98 with anterior ST-segment elevation variants. Otto and Aufderheide[13] found that less than 50% of out-of-hospital patients with chest pain and at least 1 mm of ST-segment elevation had acute myocardial infarction by elevated creatine kinase MB fraction; fewer still would have coronary occlusion (STEMI) requiring reperfusion therapy. In the most recent large registry data, 33% of STEMI patients eligible for reperfusion therapy did not receive it.[14] Similarly, Tricomi et al[15] found that, in 34% of STEMI patients who did not receive reperfusion, the reason was failure to recognize ST-segment elevation.

Two additional studies specifically evaluated physicians' abilities to differentiate STEMI from early repolarization or STEMI lookalikes. Jayroe et al[16] distributed difficult ECGs to 15 expert electrocardiographers (all cardiologists), with a clinical scenario suggestive of ischemia. There were 108 nonischemic ECGs with ST-segment elevation of various causes and 8 STEMIs; in 4 cases, the differential diagnosis was normal anterior ST-segment elevation versus early repolarization. Mean sensitivity and specificity were 75% and 85%, respectively, among these very sophisticated readers. Along similar lines, Turnipseed et al[17] distributed 25 ECGs (13 early repolarization, 12 STEMI) to 12 emergency physicians and 12 cardiologists; readers were given the patient age, sex, and race and asked to interpret the ECGs as early repolarization or STEMI. "Undercalls" (STEMI misdiagnosed as early repolarization) and "overcalls" (early repolarization misdiagnosed as STEMI) were calculated for each physician group; cardiologists correctly interpreted 90% of ECGs and emergency physicians, 81%. Undercalls and overcalls were, respectively, 3% and 17% for cardiologists and 10% and 28% for emergency physicians.

Various ST-segment elevation criteria for anterior myocardial infarction have been proposed, with recommendations usually for measurement made at the J point.[18-21] Two studies based on angiographic outcomes showed poor sensitivity of the ST-

segment elevation criteria, particularly in the circumflex territory.[3,22] Another study using magnetic resonance imaging–based outcome[23] also showed poor utility of ST-segment elevation criteria in the diagnosis of ST-segment elevation. All other studies we are aware of used a biomarker-based definition for myocardial infarction, resulting in questionable conclusions.[19,24-31]

We hypothesized that, in addition to ST-segment elevation, T-wave amplitude to R-wave amplitude ratio (T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$) and R-wave amplitude (R-wave amplitude) in leads V2 to V4 would help differentiate STEMI from early repolarization on ECG. Secondarily, we hypothesized that the Bazett QTc (QT interval/[square root of R-R interval]) would be an important discriminator. We also hypothesized that there would be a higher degree of upward concavity in early repolarization than in myocardial infarction.

Goals of This Investigation

We sought to identify ECG measurements that differentiate nonobvious, or "subtle," anterior STEMI from early repolarization, with special attention to T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$, R-wave amplitude, QTc interval, and ST-segment elevation.

MATERIALS AND METHODS

Study Design

We conducted a retrospective cohort analysis comparing nonobvious (subtle) ECGs of patients who presented with STEMI and underwent primary percutaneous coronary intervention with confirmed left anterior descending occlusion with ECGs from emergency department (ED) patients with noncardiac chest pain coded as early repolarization. Results for an initial derivation group were obtained and then evaluated subsequently in a separate validation group.

Setting

The study was undertaken at Hennepin County Medical Center, an urban Level I trauma center with an approximate annual census of 95,000, and at the Minneapolis Heart Institute at Abbott Northwestern Hospital, which has a large regional STEMI network with approximately 500 STEMI patients per year presenting for primary percutaneous coronary intervention.[32] Institutional review board approval was obtained at both institutions; the study was deemed exempt from formal review because it involved only review of existing records.

Selection of Participants

For the derivation group, we searched the database of Minneapolis Heart Institute for all patients who were admitted with the diagnosis of acute anterior STEMI from March 2003 to October 2004.[33] We also searched the catheterization laboratory database at Hennepin County Medical Center for anterior STEMI patients treated from March 2003 to April 2005. For the validation group, we similarly searched the Minneapolis Heart Institute database from November 2004 until October 2005 and Hennepin County Medical Center from May 2005 through March 2009. We selected all patients with acute anterior STEMI confirmed by coronary angiography with acute left anterior descending occlusion with TIMI 0/1 flow. No patient was enrolled more than once.

We reviewed the "diagnostic" ECG that resulted in catheterization laboratory activation. We excluded patients with bundle-branch block and, to concentrate on the difficult or subtle ECGs, we excluded those with obvious electrocardiographic STEMI (ST-segment elevation >5 mm, nonconcave morphology [ie, convex, or "coved," morphology], greater than or equal to 1 mm of summed inferior [leads II, III, and aVF] ST-segment depression,[34,35] anterior ST-segment depression, terminal QRS distortion, Q waves in any of V2 to V4, or T-wave inversion in any of V2 to V6). Terminal QRS distortion has been associated with STEMI and with adverse outcomes and was determined if the QRS slurred into the ST-segment without any S wave or J wave.[3,36] "Nonconcave" morphology was defined as follows: for all of leads V2 to V6, a straight line was placed from the J point to the inflection of the T wave near its peak. If there is area below that line, it is "concave;" conversely, if there is no area, then the ST-segment is either straight or convex, these latter 2 being combined as nonconcave. An ECG was coded as concave only if all 5 leads from V2 to V6 were concave.[3,37]

We searched the ECG database for consecutive patients who presented to the Hennepin County Medical Center Emergency Department with chest pain and whose ECG results were coded by cardiologists as "early repolarization." The derivation group included patients presenting from January 2003 to August 2004; the validation group included patients from April 2004 to June 2005. We reviewed all records and included patients whose final chest pain diagnosis was nonischemic and included at least 3 serial negative cardiac troponin I markers. For multiple ECGs on the same patient, only the first ECG from the first ED presentation with chest pain was used. ECGs were then excluded if there was not at least 1 mm of ST-segment elevation in any of leads V2 to V4.

Paper ECGs for all patients identified were collected and measured by hand. The measurements made and analyzed were those relevant to our hypotheses. Measurements for the derivation group, except for upward concavity, upright T-wave, and J-wave notching measurements, were conducted independently by an internal medicine resident (A.K.) and an emergency medicine resident (K.H.) who were part of the research team and aware only of the R-wave hypothesis. Because of institutional differences in appearance of the ECGs, these readers were not completely blinded to the diagnosis. An additional reader of ST-segment elevation at the J point and 60 ms after the J point in leads V1, V5, and V6 was a medical student (E.S.) unaware of the study objectives.

ST-segment elevation at the J point and ST-segment elevation 60 ms after the J point were both measured because

they have been shown to be very different.[38] ST-segment elevation at the J point, ST-segment elevation at 60 ms after the J point, R-wave amplitude in millimeters, and T-wave amplitude were measured to the nearest 0.5 mm in each of V1 to V6, relative to the PR segment. There is no standard method of ST-segment elevation measurement in thrombolytic trials, and the standardized reporting guidelines do not state whether to measure relative to the PR or TP segment.[38,39] Interrater reliability for this measurement technique has been previously reported for STEMI[38,40] and was assessed in early repolarization cases in the present study by comparing measurements made independently by K.H. and A.K. for ST-segment elevation at the J point and 60 ms after the J point, R-wave amplitude, T-wave amplitude, and T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$ in the derivation group. The mean T-wave amplitude$_{avg}$:R-wave amplitude$_{avg}$ ratio was calculated as mean R-wave amplitude in leads V2 to V4/mean T-wave amplitude in leads V2 to V4. The computerized QTc was recorded; it measures the longest of the 12 QT intervals on the 12-lead ECG, and in the normal range it is more accurate than manual measurement.[41] Bazett correction divides by the square root of the R-R interval, measured in seconds. Computerized ECG interpretation algorithms varied among the many referring hospitals.

Upward concavity was independently measured by 2 readers (M.R. and R.J.C.) in each of leads V2 to V4 by drawing a line from the J point to the upwardly convex inflection point along the slope of the T wave (the tangent line, T). Then the longest perpendicular line (P) from the T line to the tracing was drawn. T and P were measured to the nearest 0.25 mm with a ruler. Upward concavity was computed as P/T. Interrater reliability for P, T, and upward concavity was computed in the derivation group.

Additionally, each ECG was evaluated by the lead author for an upright T wave in lead V1 and a T wave in V1 larger than the T wave in V6, which may be suggestive of anterior STEMI.[42,43] Upright T wave in V1 was defined as a T wave in V1 having no negative component. A T wave in V1 larger than a T wave in V6 had to be completely upright and have an amplitude, as measured from the PR interval, at least 1 mm greater than that in V6.

Finally, a single physician reader, blinded to objectives and outcomes, assessed J-wave notching, measured as an increase in amplitude at the end of the QRS, from base to peak to the nearest 0.25 mm, in leads V2 to V6. J-wave notching was present if greater than or equal to 0.5 mm was observed in at least 1 of the 5 leads.

Interrater reliability between the 2 readers for ECG measurements ST-segment elevation at the J point and 60 ms after the J point, R-wave amplitude, T-wave amplitude, and T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$ in early repolarization cases ranged from 0.55 to 0.96 (Appendix E1*A*, available online at http://www.annemergmed.com). For upward concavity (early repolarization and STEMI cases), coefficients for P, T, and upward concavity varied from 0.32 to 0.93 (Appendix E1*B*, available online at http://www.annemergmed.com), with measurements for the tangent (T) being more highly correlated between the readers than measurements of the perpendicular (P).

Table 1. Primary reasons for exclusion of STEMI ECGs.*

Primary Exclusion	Derivation Group	Validation Group
Number excluded	61 of 121	151 of 234
STE >5 mm	16	46
Nonconcave morphology	15	21
≥1 mm of summed inferior ST-segment depression	12	31
Anterior ST-segment depression	2	5
Terminal QRS distortion	12	28
T-wave inversion in any of V2–V6	15	26
LBBB or arrhythmia	5	12

STE, ST-segment elevation; *LBBB*, left bundle-branch block.
*Some had more than 1 primary reason for exclusion.

Data Collection and Processing

ECG measurements were summarized by means and SDs (or median) and 95% confidence intervals (CIs) for differences computed. Pearson correlation coefficients were computed to assess interrater reliability, with CIs calculated with Fishers z′ transformation. Multivariate logistic regression was used to identify ECG measurements independently predictive of STEMI (coded as 1) versus early repolarization (coded as 0) in the derivation group. ECG measurements were divided into groups (ST-segment elevation at the J point and 60 ms after the J point; T-wave amplitude, R-wave amplitude, and T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$ ratio; QTc alone; other ECG characteristics) and evaluated in turn to identify measurement(s) within each group independently differentiating STEMI from early repolarization. Independent variables from each group were then evaluated together. A variable was added to a model only if at least 5 additional (of 60) STEMIs were correctly classified, and to keep models simple, no interaction terms (effect modification) were considered. Goodness of fit was assessed with the Hosmer-Lemeshow statistic. Model concordance was measured by computing the *c* statistic. Measurements were continuous unless otherwise specified. The model derived in the derivation group was then applied to the validation group. Sensitivity, specificity, and accuracy for the derived ECG criterion were computed separately in the derivation group and validation group, with CIs computed with the exact method. Area under the receiver operating curve, positive likelihood ratio, and negative likelihood ratio were computed to assess diagnostic utility of demographic characteristics, ECG measurements, and the ECG criterion overall. All tests were 2 sided, and statistical significance was accepted at the .01 level to compensate for multiple comparisons. Statistics were computed with SPSS (version 18.0; SPSS, Inc., Chicago, IL) and MedCalc (version 11.3.0; Mariakerke, Belgium).

Table 2. Demographics and ECG measurements of derivation and validation groups combined.*

ECG Measurement	ER	MI	Difference (95% CI)
N	171	143	
Age, y	38 (10)	60 (15)	21 (18 to 24)
Male, %	86	75	−11 (−20 to −3)
STEJ and STE60, mm			
STEJ V2	1.44 (0.7)	2.21 (1.1)	0.77 (0.56 to 0.98)
STEJ V3	1.35 (0.7)	2.08 (1.3)	0.73 (0.50 to 0.97)
STEJ V4	1.10 (0.8)	1.60 (1.1)	0.50 (0.28 to 0.72)
STE60 V2	2.19 (0.9)	3.14 (1.4)	0.95 (0.68 to 1.23)
STE60 V3	2.00 (0.8)	3.15 (1.8)	1.14 (0.82 to 1.46)
STE60 V4	1.28 (0.6)	2.41 (1.6)	1.14 (0.86 to 1.41)
T-wave and R-wave amplitude, mm, and T:R ratio			
TA V2	6.5 (3.0)	7.1 (3.6)	0.6 (−0.2 to 1.3)
TA V3	6.8 (2.5)	7.4 (3.9)	0.7 (−0.8 to 1.4)
TA V4	5.6 (2.3)	6.0 (3.4)	0.4 (−0.3 to 1.0)
RA V2	5.8 (3.8)	2.5 (2.8)	−3.3 (−4.0 to −2.5)
RA V3	10.8 (6.2)	4.5 (4.5)	−6.3 (−7.5 to −5.1)
RA V4	17.6 (7.4)	7.2 (5.4)	−10.4 (−11.8 to −8.9)
TA_{avg}/RA_{avg} ratio	0.7 (0.4)	3.1 (4.3)	2.5 (1.8 to 3.2)
QTc, msec	390 (28)	426 (30)	36 (29 to 43)
Other ECG characteristics			
Upright T wave V1, %	46	73	27 (16 to 37)
T wave in V1 larger than in V6, %	15	39	24 (14 to 33)
V2 concavity†	0.11 (0.05)	0.11 (0.06)	0 (−0.01 to 0.01)
V3 concavity†	0.12 (0.05)	0.11 (0.06)	−0.01 (−0.02 to 0.003)
V4 concavity†	0.15 (0.06)	0.12 (0.06)	−0.03 (−0.04 to −0.02)
Maximum J-wave notching V2–V6, median	0.25	0	—
Any J-wave notch ≥0.5 mm, %	31	14	−17 (−26 to −8)

ER, Early repolarization; *MI*, myocardial infarction; *STEJ*, ST-segment elevation at the J point; *STE60*, ST-segment elevation 60 ms after the J point; *TA*, T-wave amplitude; *RA*, R-wave amplitude.
*Values shown are means (SD) unless otherwise indicated.
†Perpendicular measurement divided by tangent measurement.

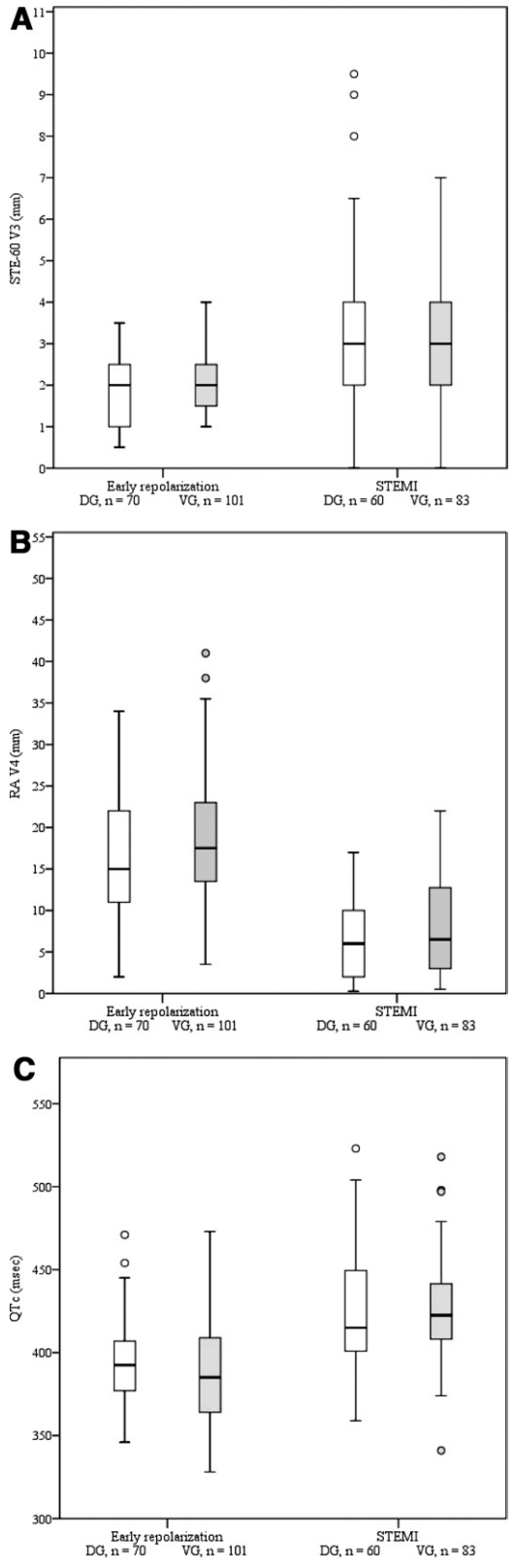
RESULTS

There were 121 patients identified with documented anterior STEMI with left anterior descending occlusion for the derivation group: 60 had subtle STEMI ECGs (50%) and were included in the analysis, and 61 were excluded for 1 or more reasons (Table 1). Of the 234 patients with STEMI identified for the validation group, 83 were included and 151 were excluded (Table 1). There were 100 potential patients in the derivation group early repolarization ECGs, 70 were included in the analysis, and 30 were excluded because of absence of 1-mm ST-segment elevation in at least 1 of leads V2 to V4. Of the 142 validation group early repolarization ECGs reviewed, 101 were included and 41 were excluded for the same reason. Of the 171 early repolarization patients with ST-segment elevation, 6 had either nonconcave ST-segments or T-wave inversion in a least 1 of leads V2 to V6.

Characteristics for the derivation group and validation group groups combined are shown in Table 2 and separately in Appendix E2 (available online at http://www.annemergmed.com). STEMI patients were on average about 20 years older than those with early repolarization and less often men. ST-segment elevation in leads V2 to V4, whether measured at the J point or at 60 ms after the J point, was higher in STEMI cases compared with early repolarization cases. We confirmed the hypothesized difference in T-wave $amplitude_{avg}$/R-wave $amplitude_{avg}$ ratio, but the difference observed was due almost entirely to the differences in R-wave amplitude. R-wave amplitude in leads V2 to V4 was lower, whereas T-wave amplitude was not importantly different. QTc was longer for STEMI versus early repolarization.

Of the 6 measurements in the ST-segment elevation at the J point and ST-segment elevation 60 ms after the J point group (Table 2), ST-segment elevation 60 ms after J point V3 was the best at differentiating STEMI versus early repolarization (odds ratio [OR] per 1-mm increase 2.5; 95% CI 1.7 to 3.8) in the derivation group (Figure 1). Of the 7 in the T-wave/R-wave amplitude/T-wave $amplitude_{avg}$/R-wave $amplitude_{avg}$ ratio group, R-wave amplitude V4 was the best (OR per 5-mm decrease 3.8; 95% CI 2.4 to 6.2), and in the "other ECG characteristics" group, T wave in V1 larger than in V6 was best (OR 3.1; 95% CI 1.4 to 6.9). Within each group, no other measurement in that group was additionally useful for differentiating STEMI versus early repolarization, ie, did not correctly classify an additional 5 myocardial infarctions regardless of statistical significance. QTc was alone in its group (OR per 10-mm increase 1.5; 95% CI 1.3 to 1.8).

In a multivariate logistic regression model of the derivation group, with measurements ST-segment elevation 60 ms after



the J point V3, R-wave amplitude V4, QTc, and T wave in V1 larger than in V6 included, each measurement was independently important in differentiating STEMI versus early repolarization, except for T wave in V1 larger than in V6.

Results of the equation ([1.196×ST-segment elevation 60 ms after the J point V3 in mm]+[0.059×QTc in ms]–[0.326×R-wave amplitude V4 in mm]) greater than 23.4 predicted STEMIs and less than or equal to 23.4 predicted early repolarization. Sensitivity, specificity, and accuracy in the derivation group for this ECG criterion were 92% (95% CI 82% to 97%), 89% (95% CI 79% to 95%), and 90% (95% CI 84% to 95%), respectively. Forward stepwise logistic regression modeling (and confirmed with backwards modeling) considering all of the measurements in the 4 groups of Table 2 identified the same 3 measurements. The *c* statistic increased from 0.858 to 0.926 to 0.963 with R-wave amplitude V4 and then the addition of ST-segment elevation 60 ms after J points V3 and QTc, respectively. The Homer-Lemeshow goodness-of-fit statistic for the final model was 8.78 ($P=.36$).

In the validation group, the sensitivity, specificity, and accuracy of this ECG criterion were 82% (95% CI 72% to 90%), 92% (95% CI 85% to 97%), and 87% (95% CI 81% to 92%), respectively. Overall sensitivity, specificity, and accuracy for this ECG criterion were 86% (79, 91), 91% (85, 95) and 88% (84, 92), respectively. For persons older than 35 years (n=249; 135 myocardial infarctions), sensitivity and specificity were 87% (95% CI 80% to 92%) and 87% (95% 79% to 92%), respectively, for the ECG criterion; for persons aged 35 years or younger (n=65; 8 myocardial infarctions), sensitivity and specificity were 75% (95% CI 35% to 97%) and 98% (95% CI 91% to 100%), respectively.

Diagnostic utility for each of these 3 measurements (ST-segment elevation 60 ms after J point V3, QTc, and R-wave amplitude V4), as well as several others for the combined derivation group and validation group, is shown in Table 3. Cut points for age and continuous ECG measurements were selected to optimize sensitivity to STEMI, ie, greater than 95%. None of the single measurements, only the ECG criterion combination of the 3 measurements (use of the 3 variable equation), had a positive likelihood ratio approaching 10, indicative of the odds

Figure 1. Box plots (median and interquartile ranges) of ECG measurements RA V4, QTc, and STE60 V3 by outcome and group. *A*, Box plots of STE at 60 ms after the J point in lead V3 in MI versus ER in derivation and validation groups. *B*, Box plots of R-wave amplitude in lead V4 in MI versus ER in derivation and validation groups. *C*, Box plots of corrected computerized QT interval in milliseconds in MI versus ER in derivation and validation groups. Bottom and top of boxes represent the 25th and 75th percentiles. Bolded line represent the median (50th percentile). Lines extend to the farthest data points within 1.5 times the height of the box. Values lying beyond the whiskers are shown as circles.

Table 3. Diagnostic utility of age, sex, and select ECG measurements for anterior STEMI with cut point optimized for sensitivity (>95%).*

Demographic or ECG Measurement	Area Under the Receiver Operating Curve (95% CI)	LR+ (95% CI)	LR– (95% CI)
Age >35 y	0.88 (0.84–0.92)	1.4 (1.1–1.8)	0.2 (0.03–0.2)
Male	0.56 (0.50–0.61)	na	na
Mean STEJ V2–V4 >0.5 mm	0.70 (0.65–0.75)	1.0 (0.6–1.7)	0.6 (0.3–1.3)
STE60 V3 >0.5 mm	0.70 (0.65–0.75)	1.0 (0.4–2.3)	2.2 (1.1–4.1)
Mean STE60 V2-V4 >1.0 mm	0.75 (0.69–0.79)	1.1 (0.7–1.7)	0.5 (0.2–1.0)
Mean RA V2-V4 <11.7 mm	0.87 (0.83–0.91)	1.7 (1.5–2.1)	**0.1 (0.05–0.2)**
RA V4 <17 mm	0.87 (0.83–0.91)	1.8 (1.5–2.1)	**0.08 (0.03–0.2)**
Mean TA >2.5 mm	0.53 (0.48–0.59)	1.0 (0.3–3.0)	2.8 (1'.4–5.7)
V4 concavity <0.22	0.65 (0.59–0.70)	1.1 (0.7–1.6)	0.5 (0.3–1.0)
QTc >384 msec	0.82 (0.77–0.86)	1.7 (1.4–2.0)	**0.1 (0.05–0.2)**
T wave in V1 larger than in V6	0.65 (0.59–0.70)	1.1 (0.6–1.7)	0.5 (0.2–1.0)
ECG criterion† >22.07	0.96 (0.92–0.98)	5.4 (5.0–5.9)	**0.06 (0.03–0.1)**
ECG criterion† at less sensitive, more specific cut point (>23.40)	0.96 (0.92–0.98)	**9.2 (8.5–10)**	**0.1 (0.08–0.3)**

LR+, Positive likelihood ratio; *LR–*, negative likelihood ratio.
*Data for derivation and validation groups were combined. Data for LR+ approaching 10 and LR– approaching 0.1 have been bolded.
†(1.196×STE60 in V3)+(0.059×QTc)–(0.326×RA in V4). QTc is the computerized QTc measured in milliseconds. RA in V4=R-wave amplitude in lead V4 in millimeters. STE60 in V3=STE as measured at 60 ms after the J point in millimeters, relative to the PR segment, in lead V3.

Table 4. Diagnostic utility of various STEMI voltage criteria in subtle myocardial infarction versus early repolarization, derivation group and validation group combined (n=314; 143 STEMI, 171 ER).*

At Least 2 Consecutive Leads With STE	Location of STE Measurement	LR+ (95% CI)	LR– (95% CI)
1) ≥1 mm V1–V6	STEJ	1.0 (0.7–1.5)	0.9 (0.5–1.4)
	STE60	1.0 (0.9–1.0)	5.0 (0.6–45)
2) ≥2 mm in any of V1–V3 or ≥1 mm V4–V6[19]	STEJ	1.4 (1.1–1.6)	0.7 (0.5–0.9)
	STE60	1.2 (0.9–1.5)	0.6 (0.4–0.9)
3) ≥1 mm V1 or V4–V6, or ≥2 mm in V2–V3	STEJ	1.3 (1.0–1.5)	0.7 (0.6–0.9)
	STE60	1.2 (0.9–1.5)	0.5 (0.3–0.8)
4) ≥1 mm V1 or V4–V6, or ≥2 mm in V2–V3 (men) or ≥1.5 mm in V2–V3 (women)	STEJ	1.3 (1.0–1.6)	0.7 (0.5–0.9)
	STE60	1.1 (0.8–1.5)	0.5 (0.3–0.8)
5) ≥1 mm in V1 or V4–V6, or ≥2 mm in V2–V3 (men) or ≥2.5 mm in V2–V3 (men <40 y) or ≥1.5 mm in V2–V3 (women)[18]	STEJ	1.5 (1.2–1.7)	0.6 (0.3–0.8)
	STE60	1.2 (0.9–1.6)	0.3 (0.2–0.6)
6) ≥1 mm in V5–V6 or ≥2 mm in V1–V4	STEJ	1.7 (1.4–2.0)	0.7 (0.5–0.9)
	STE60	1.3 (1.0–1.6)	0.5 (0.4–0.8)
ECG criterion: STEMI if >23.4: (1.196×STE60 V3)+(0.059×QTc)–(0.326×RA V4)		**9.2 (8.5–10)**	**0.1 (0.08–0.3)**

*Data for LR+ approaching 10 and LR– approaching 0.1 have been bolded.

of an ECG with these characteristics being 10 times more likely to be observed in a subtle STEMI versus early repolarization case. R-wave amplitude V4 less than 17 mm, QTc greater than 384 ms, and the ECG criterion each had a negative likelihood ratio less than 0.1, indicative of a low likelihood in a subtle STEMI versus early repolarization ECG.

None of the STEMI voltage criteria demonstrated ability to differentiate between STEMI versus early repolarization (Table 4). Interrater reliability (Appendix E1*A*, available online at http://www.annemergmed.com) was excellent (0.88; 0.81 to 0.92) for R-wave amplitude V4 and good (0.65; 0.49 to 0.77) for ST-segment elevation 60 ms after J point V3. Little agreement beyond chance between any of the STEMI voltage criteria with the ECG criterion we derived was observed (all $\kappa<0.2$; data not shown).

Figure 2 shows the application of the rule to 2 relevant ECGs with anterior ST-segment elevation.

LIMITATIONS

The ideal methodology for this study would be to enroll all patients with chest pain and ST-segment elevation and follow their course, which would require significant resources and time, ie, taking approximately 10 years at our institution to accumulate 355 anterior STEMIs while tracking thousands of patients with chest pain and early repolarization in that period. Our study is thus retrospective and on select patient groups.

The ECG diagnosis of early repolarization was determined by the cardiologist who read the ECG the next day, out of clinical context, and the interpretation was likely influenced by the age of the patient as recorded on the ECG, as well as features of the ECG known to be associated with early repolarization. The control group was limited to 1 hospital and the ECG diagnosis of early repolarization, as made by 1 cardiology group. It is possible that cases of early

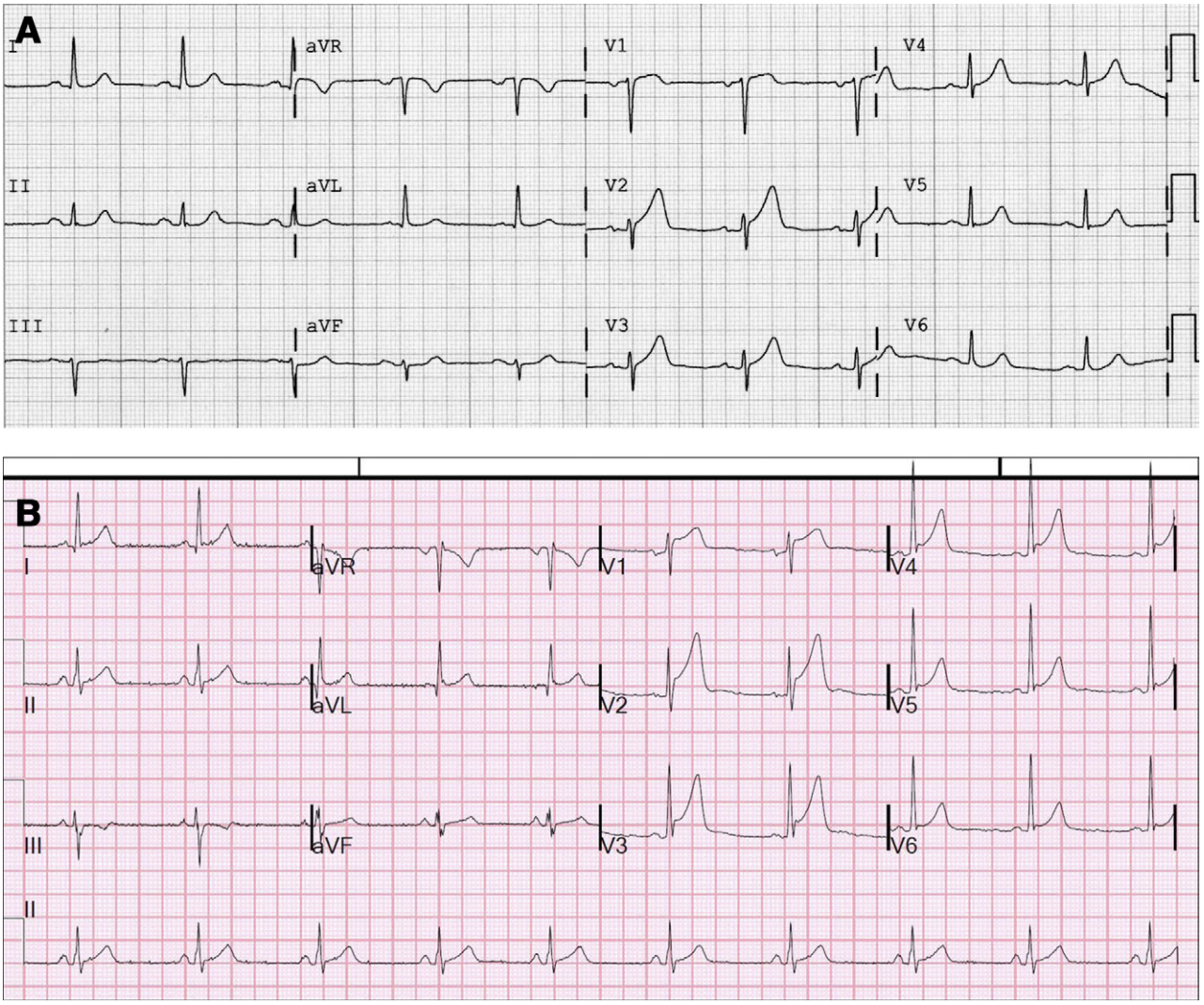


Figure 2. Typical ECGs with application of the derived ECG criterion. Neither was included in the derivation or validation group. All measurements are in millimeters. *A*, ECG of a 47-year-old man with chest pain caused by early acute left anterior descending artery occlusion. The physicians did not recognize it. Computerized QTc=411 ms. ECG criterion: (1.196×STE60 in V3)+(0.059×QTc)–(0.326×RA in V4)=1.794+24.249–2.282=23.761. Value greater than 23.4 correctly predicts STEMI. STEMI voltage criteria: Criterion 1 (≥1 mm in 2 consecutive leads of V1 to V6) correctly predicts STEMI. Rules 2 to 6 incorrectly predict ER. *B*, ECG of 34-year-old man with chest pain ruled out for myocardial infarction. Computerized QTc=371 ms. ECG criterion: (1.196×3.5)+(0.059×371)–(0.326×19)=4.186+21.889–6.194=19.881. Value less than 23.4 correctly predicts ER. STEMI voltage criteria: All criteria 1 to 6 incorrectly predict STEMI.

repolarization in older patients were not coded as early repolarization by the cardiologist, and these ECGs thus would not have been identified in our database search for early repolarization. Conversely, cases of myocardial infarction that were coded as early repolarization would have been excluded from further analysis by positive serial troponin level results (we did not keep records of these); of this group, only patients with left anterior descending occlusion would have been included (in the STEMI group, however, through the separate search). Non-STEMIs that the cardiologist coded as early repolarization and that had no occlusion on the angiogram would not have been included in either group. Occlusions that were not referred for primary angioplasty because the ECG was entirely missed also would not have been identified. Furthermore, it is likely that other subjective features of the ECG that we have not identified or measured helped the practitioner differentiate early repolarization from STEMI. All cases of early repolarization were of enough concern for the treating physicians to rule out acute myocardial infarction with 3 serial cardiac troponin markers, which required a minimum of 8 hours of assessment and, at our institution, admission to a chest pain unit. We did not collect data on race, which may be important in the diagnosis of early repolarization.

All of our ECG readers were not entirely blinded to all the objectives of the study and to the outcome of the patient whose ECG they were measuring. The age of the patient recorded on the ECG was also visible to the reader. There is additionally some risk that QTc was confounded by sex; we did not correct for this. We attempted to minimize any potential bias by having 2 readers. Additionally, there were no interrater reliability data collected on upright T-wave and J-wave notching measurements, and interrater reliability was less than optimal for some readings, likely indicative of the difficulty of manually measuring ECGs by hand.

Finally, it is important to apply these findings only when the ECG differential is anterior STEMI versus early repolarization. Analysis of ECGs with ST-segment elevation from left ventricular hypertrophy or other pseudoinfarction patterns may have very different results.

DISCUSSION

Patients with ischemic symptoms frequently have baseline ST-segment elevation on the ECG precordial leads, sometimes referred to as benign early repolarization, a "normal variant." In fact, because some ST-segment elevation is present in most individuals, baseline ST-segment elevation is not a "variant" at all.[5] The presence of baseline ST-segment elevation can make the diagnosis of STEMI in patients with ischemic symptoms difficult.

This is a challenging issue and therefore infrequently studied. In clinical practice, results for patients who have STEMI that looks like early repolarization and do not receive immediate angiography but rule in for myocardial infarction will be called "non-STEMI." These patients will be denied timely reperfusion therapy, and potentially have significant myocardial loss, but the oversight will not be detected by any study, database, or quality review. Conversely, results for patients who have early repolarization and receive catheterization laboratory activation are not generally tabulated, or if patients have coronary disease on angiogram or positive biomarker results, their results are considered a true positive, whether or not the artery was occluded and the ST-segment elevation was a result of acute coronary syndrome.

We sought to determine ECG characteristics that would discriminate ST-segment elevation caused by early repolarization (normal ST-segment elevation) from that due to STEMI but resembling early repolarization. We excluded ECGs with ST-segment elevation immediately recognizable as caused by STEMI, ie, those with massive ST-segment elevation, anterior or inferior ST-segment depression, convex or straight morphology, T-wave inversion, or terminal QRS distortion, and concentrated on the subtle ECGs. Of 355 STEMIs screened, 212 were obvious and 143 were subtle. The ECG criterion equation we derived detected 123 of the 143 subtle ones; the exclusion criteria detected the other 212. Six patients in the early repolarization group had the exclusion criteria. Thus, including the exclusions, 335 of 355 anterior STEMIs (94%) were detected and 149 of 171 early repolarization (87%). Although not perfect, these criteria are far better than the use of any of the many currently used ST-segment elevation criteria. A major strength of our study was deriving the ECG criterion in one group of patients and subsequently validating it in a second, separate group.

To our knowledge, there has been no previous attempt to systematically differentiate early repolarization from anterior STEMI on the ECG. Furthermore, to our knowledge, this is the third (and largest) study to use angiographic outcomes to evaluate ST-segment elevation measurements in acute myocardial infarction.[3,22]

Brady et al[37] attempted to use "morphologic criteria" (upward concavity) to differentiate normal ST-segment elevation from acute myocardial infarction (as diagnosed by biomarkers, not angiography) and did so with a sensitivity and specificity of 77% and 97%, respectively, but did not separately report anterior STEMI versus other locations. For anterior STEMI, nonconcave morphology has a low sensitivity (65%) and high specificity.[3,44] We assumed that all nonconcave morphology was "obvious" myocardial infarction and was excluded from the study; at least 40% had upward concavity in all of leads V2 to V5. Our results support that nonconcave morphology has poor sensitivity for anterior STEMI.

Our findings are consistent with previous literature that suggests there may be a high T-wave amplitude$_{avg}$/R-wave amplitude$_{avg}$ ratio in acute STEMI[40,45-49]; however, we found that the difference was due to the difference in R-wave amplitude. We did not confirm that the differences are due to changes in the R wave or T wave during evolution of acute myocardial infarction; they may be solely due to the higher baseline R-wave amplitude in early repolarization.

Median normal Bazett QTc is 401 msec for men and 414 msec for women, values intermediate between the average of 390 observed in our early repolarization group and 426 observed in our STEMI group.[50] However, it is known that QT interval may be prolonged in ischemic myocardium. In particular, the Bazett QTc may be lengthened during various intervals after the onset of injury.[51,52] This is the first and most sensitive change observed on the ECG after coronary balloon occlusion.[53]

Cardinal features of early repolarization include a tall R wave, upwardly concave ST-segment in all of leads V2 to V6, a distinctive J wave, an asymmetric T wave (gradual upslope, steep descent), and early R-wave transition (Figure 2*B*).[54-57] Nevertheless, it is at times difficult to make an electrocardiographic distinction between STEMI and early repolarization in the patient with symptoms suggestive of myocardial ischemia. Our study confirms the value of tall R waves in distinguishing early repolarization from subtle STEMI. Although lower degrees of upward concavity, upright T wave in V1, and T wave in V1 greater than T wave in V6 were more prevalent in the subtle STEMI versus early repolarization group, they offered little in additional diagnostic utility.

Our data suggest that commonly used voltage criteria are not accurate for anterior STEMI, regardless of criteria and whether measured at the J point or 60 ms after the J point. This result is consistent with that of the 2 other studies that evaluated ECG criteria in angiographically proven left anterior descending occlusion.[3,22] Studies of acute myocardial infarction as diagnosed by creatine kinase MB fraction also did not find an accurate ST-segment elevation cutoff and reported that a subjective analysis of the ECG was better than their measured criteria and that computerized algorithms were inaccurate in the diagnosis of acute myocardial infarction.[24-27] Nevertheless, societies promote the use of millimeter criteria to diagnose STEMI.[58] The American College of Emergency Physicians 2006 guidelines state that indications for reperfusion therapy (thrombolytics or percutaneous coronary intervention) are "ST elevations greater than or equal to . . . 0.2 mV (2 mm) in 2 or more contiguous *precordial* leads lacking features of non-infarction causes of ST-segment elevation (eg, early repolarization. . .)"[59]; however, no guideline is given on differentiating STEMI from early repolarization.

An online calculator for the multivariate equation can be found on the right-hand side of Dr. Smith's[60] ECG blog (http://hqmeded-ecg.blogspot.com).

R-wave amplitude is lower in subtle (ie, not clearly diagnostic) STEMI than in early repolarization and is the single most important distinguishing variable, better than ST-segment elevation. Each of the 3 findings of upright T wave in V1, T wave in V1 greater than T wave in V6, and J-wave notching distinguish the 2 entities but are much inferior. The combination of R-wave amplitude, QTc, and ST-segment elevation (at 60 ms after the J point) measurements can distinguish subtle STEMI from early repolarization with high sensitivity and specificity. R-wave amplitude is lower, ST-segment elevation greater, and QTc longer for subtle anterior STEMI versus early repolarization. In combination with other clinical data, this criterion could be an important adjunct in the diagnosis of anterior STEMI, and because ECG measurements are increasingly analyzed by computer algorithms, implementation would not be difficult.

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Appendix E1A. Interrater reliability (Pearson correlation coefficient) for measurements of ST-segment elevation at the J point, ST-segment elevation 60 ms after the J point, R-wave amplitude, T-wave amplitude, and TA_{avg}/RA_{avg}, from early repolarization cases of the derivation group.*

	Lead		
Measurement	**V2**	**V3**	**V4**
STEJ	0.83 (0.74–0.89)†	0.69 (0.54–0.80)	0.55 (0.36–0.70)
STE60	0.76 (0.64–0.84)	0.65 (0.49–0.77)	0.66 (0.50–0.77)
RA	0.93 (0.89–0.96)	0.96 (0.94–0.98)	0.88 (0.81–0.92)
TA	0.94 (0.91–0.96)	0.84 (0.75–0.90)	0.86 (0.78–0.91)
TA_{avg}/RA_{avg}	0.79 (0.68–0.86)	0.96 (0.94–0.98)	0.96 (0.94–0.98)

Appendix E1b. Interrater reliability (Pearson correlation coefficient and 95% CIs) for measurements of "upward concavity" from both early repolarization and STEMI cases in the derivation group.

Tangent	0.92 (0.90–0.94)	0.93 (0.91–0.94)	0.90 (0.88–0.92)
Perpendicular	0.49 (0.40–0.57)	0.75 (0.70–0.79)	0.80 (0.76–0.84)
Concavity‡	0.32 (0.22–0.42)	0.53 (0.45–0.61)	0.56 (0.48–0.63)

*Interrater reliability for these measurements in STEMI has been previously published.[37,39]
†Data are 95% CI.
‡Perpendicular measurement divided by tangent measurement.

Appendix E2. Demographics and ECG measurements by patient group.*

	Derivation Group		Validation Group	
Measurement	**ER**	**MI**	**ER**	**MI**
N	70	60	101	83
Age, y	40 (9)	61 (16)	37 (11)	59 (14)
Men, %	91	76	82	74
STEJ V2	1.5 (0.8)	2.4 (1.2)	1.4 (0.7)	2.1 (1.0)
STEJ V3	1.3 (0.7)	2.3 (1.3)	1.4 (0.7)	1.9 (1.2)
STEJ V4	1.0 (0.6)	1.7 (1.1)	1.2 (0.9)	1.5 (1.2)
STE60 V2	2.1 (0.9)	3.4 (1.6)	2.3 (0.9)	3.0 (1.4)
STE60 V3	1.8 (0.8)	3.4 (2.0)	2.1 (0.8)	3.0 (1.6)
STE60 V4	1.2 (0.6)	2.5 (1.8)	1.3 (0.6)	2.3 (1.4)
RA V2	5.6 (4.0)	2.7 (3.1)	5.9 (3.7)	2.4 (2.6)
RA V3	10.9 (6.6)	5.0 (4.9)	10.7 (5.9)	4.1 (4.2)
RA V4	16.4 (7.5)	6.9 (4.7)	18.4 (7.3)	7.4 (5.8)
TA V2	6.5 (3.2)	7.4 (4.0)	6.5 (3.0)	6.8 (3.3)
TA V3	6.6 (2.8)	7.5 (3.8)	6.9 (2.3)	7.4 (4.0)
TA V4	5.4 (2.7)	5.8 (3.4)	5.8 (1.9)	6.1 (3.4)
TA_{avg}/RA_{avg} ratio	0.67 (0.39)	2.4 (2.0)	0.64 (0.38)	3.7 (5.3)
QTc	394 (24)	420 (26)	387 (29)	430 (33)
Upright T wave in V1, %	54	68	40	76
T wave in V1 larger than in V6, %	19	42	12	36
V2 concavity†	0.11 (0.04)	0.11 (0.07)	0.11 (0.05)	0.10 (0.06)
V3 concavity†	0.12 (0.05)	0.10 (0.06)	0.12 (0.05)	0.11 (0.07)
V4 concavity†	0.14 (0.07)	0.11 (0.06)	0.15 (0.05)	0.12 (0.07)
Maximum J-wave notching V2–V6, median	0.13	0.00	0.25	0
Any J-wave notch ≥0.5 mm, %	33	13	30	15

*Values shown are means (SD) unless otherwise indicated.
†Perpendicular measurement divided by tangent measurement.